

Functional Neuroimaging Studies of Motor Recovery After Stroke in Adults

A Review

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Background—The precise mechanisms of and biological basis for motor recovery after stroke in adults are still largely unknown. Reorganization of the motor system after stroke as assessed by functional neuroimaging is an intriguing but challenging new field of research. Provocative but equivocal findings have been reported to date.

Summary of Review—We present an overview of functional neuroimaging studies (positron emission tomography or functional MRI) of motor tasks in patients recovered or still recovering from motor deficit after stroke. After a brief account of the connectivity of motor systems and the imaging findings in normal subjects, the literature concerning stroke patients is reviewed and discussed, and a general model is proposed.

Conclusions—Both cross-sectional and longitudinal studies have demonstrated that the damaged adult brain is able to reorganize to compensate for motor deficits. Rather than a complete substitution of function, the main mechanism underlying recovery of motor abilities involves enhanced activity in preexisting networks, including the disconnected motor cortex in subcortical stroke and the infarct rim after cortical stroke. Involvement of nonmotor and contralesional motor areas has been consistently reported, with the emerging notion that the greater the involvement of the ipsilesional motor network, the better is the recovery. This hypothesis is supported by the enhanced activity of the ipsilesional primary motor cortex induced by motor training and acute pharmacological interventions, in parallel with improved motor function. Further longitudinal studies assessing the relationships between such changes and actual recovery, as well as manipulating such changes by rehabilitation or pharmacological maneuvers, should provide further information on these fundamental questions. This review closes with some perspectives for future research. (*Stroke*. 2003;34:1553-1566.)

Key Words: cerebral blood flow ■ magnetic resonance imaging, functional ■ recovery of function ■ stroke ■ tomography, emission computed

Despite recovery, stroke is a leading cause of disability, with more than 50% of patients being left with a residual motor deficit, especially a deficit affecting the hand.¹ Although across patients recovery assumes an exponential shape, with a faster initial recovery followed by a slower asymptotic pattern, individually there is considerable variability in both shape and final outcome.¹ Despite a huge body of literature on brain plasticity based on animal studies,² the mechanisms and biological basis for motor recovery in humans are still largely unknown. Most of our knowledge about recovery after stroke is observational³ because direct studies of brain function in humans have become possible only recently with the introduction of sophisticated imaging techniques such as positron emission tomography (PET) and functional MRI (fMRI) and novel electrophysiological techniques such as transcranial magnetic stimulation (TMS). In this article we review the peer-reviewed literature on motor activation studies performed with PET and fMRI in stroke

patients. Findings with TMS will be mentioned only whenever they are relevant to the scope of this review; the interested reader is referred to specific reviews.⁴⁻⁶ Apart from motor functions, other functions such as language will be referred to only to the extent that the findings are relevant to motor recovery; again, the interested reader is referred to specific reviews.⁶⁻⁸

Methodological Considerations

Experimental Paradigm and Data Analysis

In the last decade, 20 motor activation studies in which PET or fMRI was used have appeared in the literature.⁹⁻²⁸ Both subcortical and cortical stroke patients have been studied, and tasks known to elicit appropriate changes in motor networks in normal subjects were used. (See Appendices 1 and 2 for a summary of the normal anatomy and connectivity of the motor systems and the findings with PET and fMRI in normal

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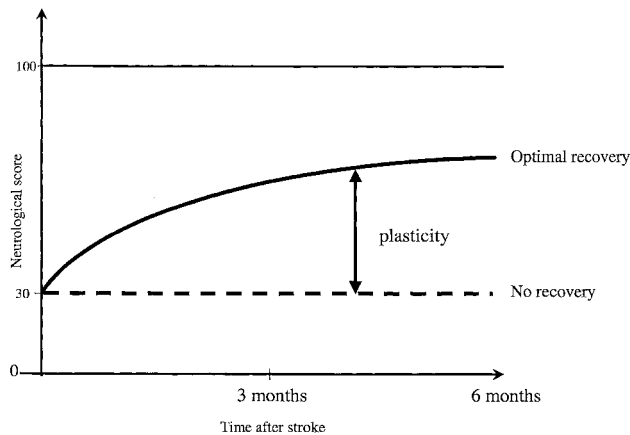


Figure 1. Idealization of time course of neurological score (100=normal function) from onset until approximately 6 months after stroke, as a function of plasticity. The 2 extremes of optimal recovery and no recovery are illustrated. Outcome at 6 months depends on lesion size and topography but can vary from poor to good depending on the degree and efficacy of plasticity (double arrow), which underlies recovery. The graph serves to illustrate the importance of assessing recovery (rather than outcome) when studying brain plasticity after stroke, since, depending on the individual lesion, a given outcome may correspond to different degrees of plasticity.

subjects. They can be found online at <http://stroke.ahajournals.org>.) To allow comparison with normal subjects, investigations initially concerned fully recovered patients studied at a single time point only, with the assumption that the differences observed in activation patterns compared with normal subjects would tell us how the damaged brain has adapted to the lesion. However, it soon became evident that such studies are not well suited to assess the role of the changes observed in the recovery process, namely, beneficial, epiphenomenal, or detrimental, or to investigate the possible occurrence of dynamic changes in the pattern of activation during the process of recovery. Accordingly, recent studies have focused on still-recovering patients,^{14,16–18,20–22,26–28} with several employing a longitudinal design.^{17,18,20–22,27,28} The longitudinal design allows investigators to study, in the same patient, the evolution of the activation pattern as recovery takes place, allowing them to relate, with greater statistical power than possible with cross-sectional studies, the changes in activation pattern over time to the actual motor recovery observed; the latter should be expressed as improvement in motor scores, which expresses the effect of plasticity, rather than final outcome, which is a function of lesion size and topography²⁹ (see Figure 1 for illustration) and especially the extent of damage of the corticospinal tract (CST).^{27,30} One potential problem with longitudinal studies, however, refers to the training effect if the motor task is complex (therefore simple tasks not involving learning are preferred)³¹ and more generally to the interference from standard rehabilitation, which cannot be avoided for obvious ethical reasons.

Two main types of paradigms can be used in fMRI studies, namely, block design and event-related design. The former has been used in almost all studies of motor recovery, while the latter has been used in a pilot study in normal subjects to assess somatosensory activation³² and recently in a study of

language recovery.³³ Although more difficult to implement, the event-related design is attractive because it allows investigators to obtain some information about the time course of activation among the motor network areas. In regard to the analysis of fMRI data sets, different approaches can be used. Simple *t* tests compare task and rest in patients and in controls but do not directly compare the 2 groups, which can be addressed with factorial designs. In addition, rather than categorical comparisons, parametric analysis such as correlation, relating the blood oxygen level–dependent (BOLD) signal to task parameters or performance, is an interesting approach to study brain function.

Quantitative indices extracted from activation patterns, such as the laterality index (LI), displacement of SM1 coordinates, and overactivation extent, and the study of their changes relative to normal subjects and over time have recently attracted considerable interest.^{12,18,22,23,26,33a} Correlations between changes over time and concomitant recovery of motor function have started to appear.^{22,28} On the basis of published studies on the effects of rehabilitative procedures and pharmacological interventions on recovery,^{3,34–38} the concept that brain plasticity can be manipulated has been applied to functional imaging recently,^{20,24,26} with important implications for enhancing recovery.

Patient-Related Issues

Application of functional imaging to stroke patients also presents some difficulties. Full cooperation of the patient is vital for head motion and task performance reasons, and therefore global cognitive impairment, aphasia, neglect, substantial sensory disturbances, and severe depression often constitute exclusion criteria. Claustrophobia is an additional exclusion criterion, especially for fMRI. Medications that may interfere with recovery and/or neurovascular coupling, such as antiepileptics, benzodiazepine, and antidepressants, should ideally be avoided. In addition to these general exclusion criteria, the age, side, and size of the lesion²⁹ may be considered to improve sample homogeneity. The severity of the motor deficit at the time of imaging should also be taken into consideration. Ideally, one wishes to study finger movements, which are the most functionally useful and depend on the integrity of the CST. The performance of the motor task during imaging should be not only monitored but also fixed across both patients and controls as well as over time in longitudinal studies for a sound comparison of the data set and thus a better interpretation of the results. However, because this would result in excluding patients with severe or complete deficit, several groups have used nonfixed paradigms or passive movements; the significance of the data from these studies, however, remains unclear (see below). Finally, 2 problems are more specific for fMRI. First, inadvertent head motion during (and correlated with) the motor task may induce false-positives and should therefore be reduced to a minimum; the data set should be reviewed before statistical analysis is begun, and the series with significant motion should be discarded. Second, major artery occlusion or severe stenosis or even perhaps small-vessel disease may affect the cerebrovascular reserve and, in turn, the neurovascular coupling on which the BOLD effect is based^{39–41};

although this does not undermine the performance of functional imaging in such patients, the risk of the data being affected should be noted, and ideally all patients should be screened for altered cerebrovascular reactivity and excluded from the protocol if necessary. Another potential confounder is the occurrence of synkinesia (ie, associated movement of other body parts) during task execution, either ipsilateral to the affected hand (usually involving proximal muscles) or contralateral to it (ie, mirror movements). Ideally, patients with severe synkinesia should be excluded from the study, or synkinesia should be continuously monitored and, if possible, recorded (eg, with video, electromyogram, or accelerometry) during or just after data acquisition. It is also advisable to exclude left-handed persons. One consequence of these constraints is that primarily very small patient samples have been studied, which furthermore may not represent the entire spectrum of deficit and recovery, and therefore replicability of results and generalization of findings are important issues.

Summary of Results

In the first section, we will describe the activations and overactivations reported first in cross-sectional and then in longitudinal studies (see also Appendices 3 and 4, which can be found online at <http://stroke.ahajournals.org>) (in this review, “activation” and “overactivation” mean “significant focal increase in relative cerebral blood flow [CBF] in the [task versus rest] comparison” and “significantly higher relative CBF when comparing [task versus rest] between patients and controls,” respectively), dealing first with cross-sectional and then with longitudinal investigations. In the second section, the findings with LI and SM1 activation displacement/extension will be reported. The third section will address the clinical correlates of the activation patterns, especially in terms of motor recovery. Finally, the effects of rehabilitation procedures and pharmacological manipulations will be described.

Cross-sectional Studies

The experimental characteristics of the studies, as well as the activation and overactivation patterns reported in each, are summarized in Tables 1, 2, and 3, respectively, and each study is detailed in Appendix 3.

The first 3 studies to appear in the literature^{9–11} were PET investigations of fully recovered patients performing a thumb-to-fingers sequential opposition task. Most subsequent studies, using either PET or fMRI, continued to investigate mainly fully recovered subcortical stroke patients during thumb-to-fingers opposition sequences or index tapping.^{12–15,19} Only few cortical stroke patients^{12,14,15} or incompletely recovered patients¹⁴ have been studied. The patient’s age was variable in most studies but well controlled in a few.^{12,13} In all studies, however, the time of scanning from stroke onset was highly variable (from days to years).

Despite different imaging technology (ie, PET or fMRI) and statistical methods (ie, voxel-based or region of interest [ROI]–based analysis), which may explain some of the differences, similar results were obtained overall from these cross-sectional studies, documenting highly significantly abnormal patterns of activation during affected-hand move-

ments, as well as differences in activation patterns between subcortical and cortical strokes. In fully recovered patients with striatocapsular infarction, the findings have consistently showed (1) enhanced bilateral activation of motor pathways, not clearly related to mirror movements; (2) recruitment of additional sensory and secondary motor structures not normally involved in the motor tasks tested; and (3) extension of SM1 activation toward the face area. In patients with cortical infarcts, a pattern of overactivation of bilateral noninfarcted motor-related and nonmotor areas similar to that seen in striatocapsular strokes has been reported. However, 2 interesting findings have been strong peri-infarct activation¹² and ipsilesional premotor cortex (PM) activation.¹⁵ Finally, whether fully recovered and still-recovering patients have different activation patterns is difficult to assess from the aforementioned studies because of both their cross-sectional design and the lack of control in nonrecovered subjects in regard to the actual performance during scanning. As will be seen below, recent longitudinal studies have addressed the issue of the dynamics of these changes as recovery is taking place.

Longitudinal Studies

Longitudinal studies are described in Tables 1, 2, and 3 and Appendix 4. Of the 5 longitudinal investigations published to date, 3 consisted of 2 functional imaging studies^{17,18,21}, 1 of 3 studies,²⁷ and 1 of 4 investigations,²⁸ but with different time points and between-assessment intervals. Thus, to date only crude estimates of the actual time course of changes have been determined. These studies used either passive¹⁷ or active motor tasks (fingers-to-thumb sequential opposition,¹⁸ thumb-to-index tapping,^{21,24} and other movements of the upper limb²⁷).

Overall, the findings from longitudinal studies of subcortical stroke^{17,18,21} are consistent with those from cross-sectional studies, especially in showing overrecruiting of motor and nonmotor areas in both hemispheres regardless of whether the task is active or passive. However, despite different paradigms and task control as well as different methodology for analysis, they also document dynamic changes; a common observation is that there is less overrecruitment in both hemispheres over time, although with individual variability. In contrast, structures such as the contralesional PM tend to develop a late overactivation, consistent with cross-sectional studies performed in the chronic stage.^{9,10,12–15} Altogether, these findings suggest that, to regain function of the affected hand, the recovery process tends to bring overactivations back toward a more normal intensity while simultaneously overrecruiting other areas, perhaps as a way to “sustain” recovery.

Two recent studies mixed cortical and subcortical stroke in their analysis^{27,28} and report only activations. In one study,²⁷ different patterns of dynamic evolution of activation were observed over time, including a “focalization” of ipsilesional SM1 found either at the first fMRI (consistently in subcortical stroke) or progressing over time (mainly in subcortical stroke) and a “recruitment” pattern with activation predominantly outside the ipsilesional SM1 (mainly seen in cortical stroke). In the other study,²⁸ which involved 4 fMRI studies,

TABLE 1. Major Characteristics of Cross-Sectional and Longitudinal Functional Imaging Studies of Motor Recovery After Stroke

Authors	Technique	Pts	Age (yrs)	Location of Lesion	Degree of Recovery	Time From Stroke	Mirror Movement	Control Group n (age)
Cross-sectional functional imaging studies								
Chollet et al ⁹	PET	6	25–71	Cortical/ subcortical	Full or good	>2 mo	Not observed	None
Weiller et al ¹⁰	PET	10	21–62	Subcortical	Full or Good	3 mo–6 yr	+ in 4 pts	10 (28–69)
Weiller et al ¹¹	PET	8	21–67	Subcortical	Full	7 w–6 yr	+ in 4 pts	10 (28–69)
Cramer et al ¹²	fMRI	10	55–86	Cortical/ subcortical	Good	11 d–15 mo	+ in 1 pt	9 (≥60)
Dettmers et al ¹³	PET	6	51–75	Supra- tentorial	Moderate to good	5 w–6 yr	Not observed	6 (mean 30)
Cao et al ¹⁴	fMRI	8	19–70	Cortical/ subcortical	Variable	5–43 mo	+ in 2 pts	8 (mean 42)
Seitz et al ¹⁵	PET	7	Mean 53	Cortical	Full	6 mo on average	Not observed	No controls
Cramer et al ¹⁹	fMRI	2	61–67	Cortical	Good	6 mo	Not observed	27 (mean 46)
Pineiro et al ²³	fMRI	8	51–78	Subcortical	Good	1–660 d	Not observed	20 (2 groups: means 28 and 67, respectively)
Cramer et al ²⁵	fMRI	7	55–86	Cortical/ subcortical	Good	11 d–14 mo	+ in 4 pts	9 (42–76)
Pariante et al ²⁴	fMRI	8	43–75	Subcortical	Good	Within 14 d	Not observed	None
Longitudinal functional imaging studies								
Nelles et al ¹⁷	PET	6	52–75	Subcortical	Variable (plegic at the 1st study)	Both PET <12 w	Not studied	3 (mean 62)
Marshall et al ¹⁸	fMRI	8	Mean 65	Lacune	Variable (some plegic at the 1st study)	1st fMRI: within 1 w 2nd fMRI: 3–6 mo	+ in 6 pts (1st study); rare at 2nd	6 (mean 30)
Nelles et al ²⁰	PET	10	Mean 68	Subcortical	Not recovered	1st PET: ~20 d 2nd PET: ~40 d	Not studied	5 (mean 63)
Calautti et al ²¹	PET	5	51–74	Subcortical	Variable, but able to perform the task at both PET studies	1st PET: ~2 mo 2nd PET: ~8 mo	+ in 2 pts (both studies)	7 (mean 60)
Carey et al ²⁶	fMRI	10	30–76	Cortical/ subcortical	Variable	1st fMRI: 0.8–21 yr 2nd fMRI 1–4 d after last training	Not studied	9 (mean 71)
Feydy et al ²⁷	fMRI	14	37–69	Cortical/ subcortical	Variable	3 fMRI over a period from 1–6 months after stroke	Not studied	None
Small et al ²⁸	fMRI	12	44–74	Cortical/ subcortical	Variable	4 fMRI (1, 2, 3, 6 mo after stroke)	Not studied	None

See Table 2 for task paradigm.

a ROI analysis revealed activation of the bilateral M1 evolving to an ipsilesional activation in all patients at the second study, with the PM, supplementary motor area (SMA), and cingulate cortex remaining activated bilaterally in some subjects in different combinations. Overall, therefore, the available data indicate a general trend for focusing of the activation toward the lesioned hemisphere SM1 as time elapses, with, however, some patients showing persistent recruitment.^{22,27} Consistent findings from longitudinal fMRI studies in a rat stroke model have been reported.⁴² Using somesthetic stimulation, the authors demonstrated that dysfunction of the hemiplegic limb was associated with loss of response in the SM1. Contralesional activity was more evident early after stroke, when sensorimotor function was

impaired, while at later stages the involvement of the ipsilesional cortex increased as sensorimotor function partially recovered.

Laterality Index

Cramer et al¹² introduced the LI as a quantitative approach in functional neuroimaging studies of stroke recovery. The LI describes the contrast in amount of activation between the unaffected and affected SM1. It is calculated as $(C-I)/(C+I)$, where C is contralateral SM1 activation volume and I is ipsilateral SM1 activation volume, and therefore LI can range from +1 (exclusively ipsilesional) to -1 (exclusively contralesional). In that study,¹² recovered patients had on average a significantly lower LI than normal subjects, indicating

TABLE 2. Activation Patterns in Cross-Sectional and Longitudinal Studies

Authors	Task	ME	Hz	Statistical Analysis	SM1		SMA		PM		Cerebellum		CMC		PFC		BA 40/BA7		Insula		Striatum	
					C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I
Cross-sectional studies																						
Chollet, et al ⁹	Thumb-to-fingers opposition	AC	1.5	Recovered hand vs rest	+	+	+	+	+	+	+	+						+	+	+	+	
				Unaffected hand vs rest	+		+	+	+		+	+								+	+	+
Cao et al ¹⁴	Thumb-to-fingers opposition	SP	Variable	Individual	7/8	6/8	2/8	2/8	1/8	6/8			6/8	3/8			2/8	6/8				
Seitz et al ¹⁵	Thumb-to-fingers opposition	SP	1.6±0.8	Individual (ROI)			+		+	+			+		+							
Pariante et al ²⁴	Hand tapping task	VC	Variable		+	+	+	+				+					+				+	+
	Passive wrist flexion-extension	AC	1	Placebo	+		+															
	Thumb-to-index tapping	AC	1	Placebo	+	+	+		+		+	+	+				+	+				
Longitudinal studies																						
Nelles et al ¹⁷	Passive elbow flexion	Passive	0.5	Group 1st PET	+					+			+		+		+	+				
	Passive elbow flexion			Group 2nd PET	+					+									+	+		
Nelles et al ²⁰	Passive elbow flexion	Passive	0.5	Group 1st PET (before arm training)															+	+		
	Passive elbow flexion			Group 2nd PET (after arm training)	+					+	+			+	+				+	+		

Ratios in brackets indicate the number of patients in whom the activation was present for each given area out of the total number of patients studied. AC indicates auditory cued; SP, self-paced; ME, modality of execution; VC, visually cued; C, contralateral to hand motion (ie, ipsilesional); I, ipsilateral to moving hand (ie, contralesional); SM1, primary motor area; SMA, supplementary motor area; PM, premotor cortex; CMC, cingulate motor cortex; PFC, prefrontal cortex; BA, Brodmann area; ROI, region of interest.

relatively greater activation of the contralesional SM1, consistent with the aforementioned general pattern of changes. Interestingly, however, some individual LI values were within the range of controls (Figure 2a). The LI values from other studies, all assessing subcortical stroke, are also shown

in Figure 2. Regarding cross-sectional studies, Pineiro et al²³ reported data very similar to those of Cramer et al¹² (Figure 2b), while in poorly recovered chronic stroke patients, Carey et al²⁶ reported more frequently negative LI values (Figure 2c). Both longitudinal studies of Marshall et al¹⁸ and Calautti

TABLE 3. Overactivation Pattern in Cross-Sectional and Longitudinal Studies

Authors	Task	ME	Hz	Statistical Analysis	SM1		SMA		PM		Cerebellum		CMC		PFC		BA 40/BA 7		Insula		Striatum				
					C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	
Cross-sectional studies																									
Weiller et al ¹⁰	Thumb-to-fingers opposition	AC	1.5	Group (recovered hand)	+					+	+	+	+	+	+	+	+	+	+	+		+			
				Group (unaffected hand)						+				+		+				+		+		+	
Weiller et al ¹¹	Thumb-to-fingers opposition	AC	1.5	Group (individual)	4/8	4/8	5/8	5/8	1/8	8/8	5/8		3/8	3/8	6/8	6/8	6/8	6/8	5/8	5/8		4/8			
Cramer et al ¹²	Index tapping	AC	2	Individual (ROI)	3/9	6/9	6/9	5/9		4/9	5/9	3/9										2/9			
Nelles et al ²⁰	Passive elbow flexion	Passive	0.5	Group*	+					+	+				+		+	+							
Longitudinal studies																									
Calautti et al ²¹	Thumb-index tapping	AC	1.26	Group 1st PET	+	+		+										+	+	+					
				Group 2nd PET	+						+														
				Individual 1st PET	3/5	2/5	1/5	2/5					3/5	3/5	2/5	1/5				3/5	4/5		1/5		
				Individual 2nd PET	2/5	2/5	1/5	2/5	2/5	2/5	2/5	1/5	1/5				1/5	2/5	1/5	1/5	1/5	1/5		1/5	2/5

Ratios in brackets indicate the number of patients in whom the activation was present for each given area out of the total number of patients studied. See Table 2 for abbreviations. *Within-patients group comparison between before and after training (see text).

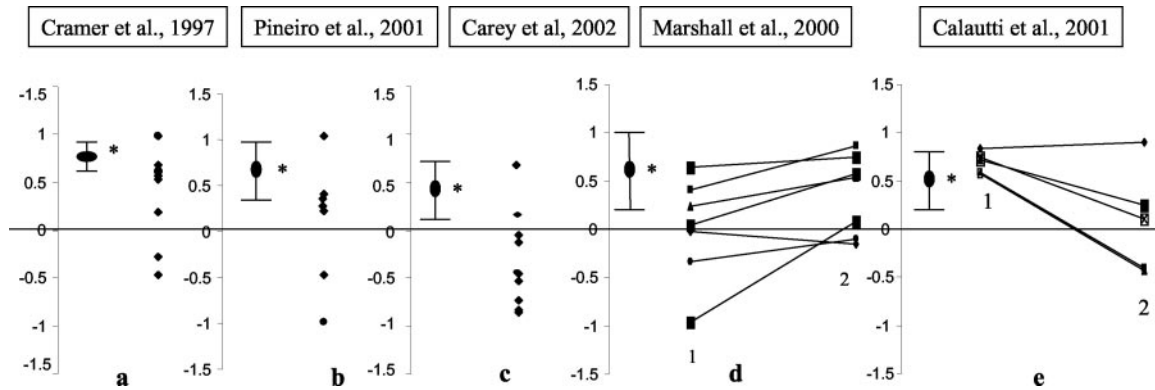


Figure 2. SM1 (a, b, c, and d) and whole-hemisphere (e) LI values in the cross-sectional studies of Cramer et al¹² (a), Pineiro et al²³ (b), and Carey et al²⁶ (c) and in the longitudinal studies of Marshall et al¹⁸ (d) and Calautti et al²² (e). For each study, the LI value for normal subjects (*) is shown as mean \pm 1 SD.

et al²² reported dynamic changes in LI values over time (Figure 2d and 2e). The former authors reported a significant mean decrease in LI at first study (at approximately 1 week after stroke) with a subsequent increase 3 to 6 months later, while the latter authors reported LI values similar to controls at first study (at approximately 2 months) but tending to decrease across subjects (although with marked individual variability; see below) at second study (6 months later). This discrepancy may reflect the different task characteristics between the 2 studies, ie, self-paced and poorly controlled in Marshall et al¹⁸ (with most patients being unable to perform the task at first fMRI) versus fixed and controlled in Calautti et al²² (Tables 2 and 3). In support of this interpretation, and as illustrated in Figure 2, the ranges of LI values obtained at second evaluation in these 2 studies were not only similar to each other but also consistent with the findings from cross-sectional studies.^{12,23,26} Another difference between these studies,^{18,22} but unlikely to explain the discrepancy, is that the LI was calculated from the SM1 and whole hemisphere data, respectively.

In summary, and as illustrated in Figure 2, a striking feature across studies is the trend for a much broader distribution of LI values in patients than in controls. Although this indicates a more frequent occurrence of prominent contralesional activation in patients, a large percentage of them exhibit LI values within the normal range, ie, there is a preserved hemispheric balance of activation. As described below, these differences in individual LI values may subtend proportional differences in recovery.

Ipsilesional SM1 Activation Coordinates

As mentioned, shifts of SM1 activation toward the infarct rim have been reported in 3 patients with cortical infarction.^{14,19} In regard to subcortical infarcts, 4 patients in the study of Weiller et al¹¹ exhibited a ventral overactivation within contralateral SM1, a finding also observed in some patients by Calautti et al²¹; this finding has also been reported after contralateral stroke in rat.⁴² In both circumstances, the putative mechanism involved has been the unmasking of hand motor representations, in analogy to the findings of Nudo et al⁴³ in monkeys. Recently, Pineiro et al²³ reported a posterior shift in SM1 geometric center activation in a group of

subcortical stroke patients, which was of similar magnitude for 2 distinct active motor tasks. The authors speculated that this could result from an intrinsic adaptive local change in the functional reorganization of the motor cortex (a locally decreased inhibition?). In a study of subcortical stroke, Calautti et al^{33a} assessed changes in SM1 activation coordinates over time, and at PET examination 1 found a significant posterior shift of affected-hemisphere SM1 activation, similar to that of Pineiro et al²³; at PET examination 2, a trend for more posterior y coordinates was still present. None of these shifts correlated significantly with motor recovery in this sample of 5 patients.

In summary, activation of peri-infarct SM1, posteriorly and inferiorly, seems to be the rule in cortical strokes. In subcortical strokes, as illustrated in Figure 3, a posterior shift was observed by both Pineiro et al²³ and Calautti et al,^{33a} suggesting consistency, although whether drifts occur over time is still unclear. This posterior shift in both cortical and subcortical strokes might represent neuronal unmasking/disinhibition within the CST; however, no correlation with recovery has been observed thus far. A different phenomenon of occasional inferior extension of SM1 activation in the disconnected cortex after subcortical stroke has been reported in 2 studies.^{11,21} Further studies in patients with different infarct sizes and sites and objective measures of recovery are required to better understand the exact meaning of these changes.

Correlation With Clinical Recovery

Only 5 studies have assessed the correlation between activation maps and motor recovery, of which 3 were longitudinal. All dealt with few patients, and therefore generalization remains uncertain. In their cross-sectional study, Seitz et al¹⁵ found no significant correlation between functional data and motor scores, even though all patients showed activation of PM and significant recovery from onset to time of PET study. Cao et al¹⁴ found no significant correlation between residual motor deficit (assessed as the time required to perform 20 finger oppositions) and the volume of activation in ipsilateral SM1. However, this was a cross-sectional study, and the performance of the motor task during fMRI was allowed to vary among patients, complicating interpretation. In their

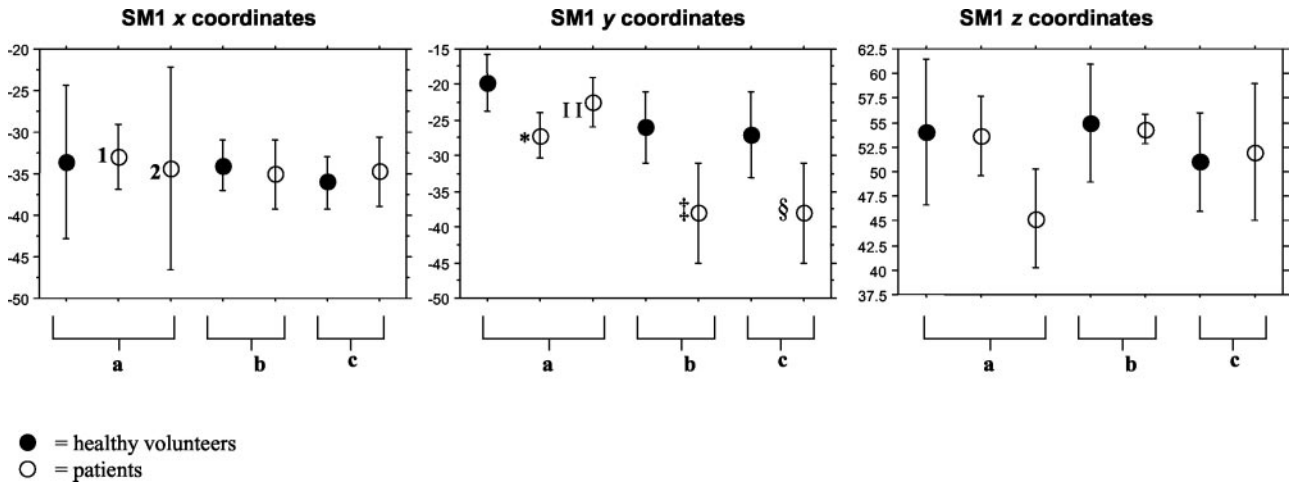


Figure 3. Mean \pm 1 SD peak coordinates (x, y, and z) of affected-hemisphere SM1 activation in healthy volunteers (black circles) and stroke patients (white circles) from the studies of Calautti et al^{33a} and Pineiro et al.²³ In both studies there was a significant posterior shift of y coordinates. For details about these studies, see Tables 2 and 3 and text. a, Thumb-index tapping, Calautti et al^{33a} (1 indicates PET examination 1; 2, PET examination 2); b, sequential finger movements, Pineiro et al²³; c, hand-tapping task, Pineiro et al.²³ * $P=0.02$; † $P=0.04$; ‡ $P=0.07$; || $P=0.08$ (all probability values relative to controls).

longitudinal study of 5 patients with subcortical stroke (see above), Calautti et al²² assessed correlations between changes in motor performance and parallel changes in LI (Δ LI). To be as close as possible to the motor task used during PET scanning (ie, fixed-rate auditory-cued thumb-index tapping), they measured the maximal number of thumb-index taps in 15 seconds, which showed significant recovery. The variability in Δ LI (Figure 2e) significantly correlated with the recovery of motor performance, such that the more the activation shifted toward the unaffected hemisphere at PET examination 2, the less was the recovery. Thus, although activation of the ipsilateral cortex may contribute to the process of recovery, it would reflect a less efficient reorganization process. Although this finding in a small sample of subcortical stroke patients and with the use of the whole hemisphere LI (see Discussion) remains preliminary, it is consistent with several descriptive reports about aphasia or neglect as well as with TMS studies (see Discussion), and with the aforementioned longitudinal fMRI study in the rat,⁴² which also suggests that recovery of function may be related to the gradual restitution of the representational neuronal fields and recruitment of perilesional networks.

Recently, Small et al²⁸ reported a weak but significant nonlinear correlation between motor performance and the volume of ipsilateral cerebellar activation, both assessed 4 times during recovery from stroke, such that the larger the ipsilateral cerebellum activation, the better was the recovery; no correlation with recovery was found for the contralateral cerebellum or for the M1 (contralesional or ipsilesional). These findings are entirely consistent with the aforementioned studies in showing that return of preferential activation toward the affected motor network (which includes the ipsilateral cerebellum) correlates with a better recovery. In addition, it is possible that better activity of the ipsilateral cerebellum after stroke reflects its postulated role in the motor learning process.^{44,45}

Feydy et al²⁷ quantified the evolution of the activation patterns with 2 indices: the “IndexSMC” (sensorimotor cortex, calculated as contralateral SM1 divided by all bilateral ROIs) and the “IndexHEM” (hemisphere, which represents the LI calculated with consideration of the whole hemisphere). When the values of these 2 indices across the 3 fMRI studies are considered, they describe 3 patterns of activation evolution (see Appendix 4). They found no clear relation between the degree of recovery and the activation pattern: the 3 patterns (“initial focusing,” “progressive focusing,” and “persistent recruitment”) were almost equally distributed among patients with good, moderate, or poor outcome. However, the pattern of focusing was nearly significantly represented to a greater extent in patients with intact M1, while in patients with M1 stroke a persistent recruitment was predominant. The authors concluded that the evolution of activation patterns was related to the severity of the M1 injury but not to the degree of recovery and that functional recovery does not depend on the type of plasticity. This provocative conclusion conflicts with the literature reviewed above but may have resulted from methodological issues, as follows: (1) performance during fMRI was controlled neither among patients nor within each patient across the fMRI sessions, with some patients only ideating or moving the shoulder; (2) the unaffected hand was used rather than a control group; (3) both dominant and nondominant hemisphere strokes were included; (4) the cutoff values of the 2 indices used to allocate patients into activation patterns are reported but not justified or validated; (5) the IndexSMC may be identical whether all nonipsilesional SM1 activation is ipsilesional or contralesional to the stroke; and (6) outcome, rather than recovery concomitant to the fMRI session, was considered.

Overall, and apart from this latter study, the available observations suggest that recovery is best when there is restitution of activation toward the physiological network

over time. Thus, rehabilitative or pharmacological interventions able to reactivate the physiological motor network should enhance recovery.

Effects of Rehabilitation

A few functional imaging studies have examined the effect on brain activation patterns of interventions that have shown benefit in randomized control trials. Using TMS, Liepert et al⁴⁶ were the first to demonstrate that after constraint-induced therapy, the motor performance of chronic stroke patients improved substantially, together with an increase of motor output area size and motor evoked potential amplitudes, indicating enhanced neuronal excitability in the damaged hemisphere for the target muscles studied. Subsequent functional neuroimaging studies used either passive or active motor tasks.^{20,26} The rationale for the former is that passive training is known to influence sensorimotor cortical representations in normal subjects⁴⁷ (see Appendix 1). A detailed account of these studies can be found in Appendix 5 (available online at <http://stroke.ahajournals.org>).

Although still preliminary, the findings overall suggest that it is possible to influence motor network reorganization after stroke by motor training procedures and that training-induced brain plasticity is possible not only in subacute but also in chronic stroke patients, ie, the time elapsed since stroke onset does not appear to be a limiting factor for this effect. Furthermore, the change in activation pattern induced by training, namely, a shift in favor of the lesioned hemisphere, is entirely consistent with the earlier findings from the nonintervention study of Calautti et al,²² as well as a subsequent TMS study from Liepert et al³⁶ (see Discussion).

Effects of Pharmacological Agents

Studies on animals have demonstrated that drugs that increase brain monoamine concentrations positively influence the rate and degree of recovery from cortical lesions; however, results are still inconsistent in clinical trials.³⁷ With the hypothesis that some antidepressants may influence outcome after stroke, a study reported that fluoxetine facilitated motor recovery when applied together with physical therapy.³⁴ A recent fMRI study²⁴ investigated the influence of a single oral dose of fluoxetine on brain activation during hand motion in patients affected by a lacunar stroke. In this double-blind, placebo-controlled, crossover trial, the authors demonstrated that fluoxetine significantly increased activation of the ipsilesional SM1 and decreased activation of the cerebellar cortex bilaterally and the contralesional caudate nucleus, SII, inferior Brodmann area (BA) 40, and inferior PM. This redistribution of activation toward affected-side motor cortex output was associated with (and linearly correlated with) enhanced motor performance (both speed and force). The design used in this study (ie, double-blind, crossover) avoids the possible influence of the drug on the BOLD effect. The authors speculated that fluoxetine, through enhanced serotonin system activity, stimulates the pyramidal cells of the M1 cortex. This enhanced activity in the affected-side primary motor cortex induced by pharmacological intervention is in accordance with the aforementioned findings regarding natural history and training effects, thereby opening new approaches

to improving recovery by means of both drugs and physical therapy.

Discussion

Even though the precise mechanisms of and biological basis for recovery remain largely unknown, functional imaging has provided important new information about motor recovery after stroke. From the aforementioned studies, several robust and mutually coherent findings seem to emerge, as follows: (1) displacement/extension of affected-side SM1 activation, ie, caudal and posterior in subcortical stroke and infarct rim in cortical stroke; (2) bilaterality of SM1 activation; (3) increased activity in primary and secondary motor areas, eg, in the bilateral PM in the late phase of recovery, as well as in some nonmotor areas, eg, late prefrontal activation; (4) shifts of activation balance between the affected and unaffected hemispheres as recovery takes place, together with decreasing amount of overactivated voxels on both sides; (5) better recovery from subcortical stroke if affected-side activation becomes predominant over time; and (6) parallel enhancement of motor performance and affected-side SM1 activation by intensive rehabilitation training and fluoxetine. Although some of the issues raised by these observations have already been addressed in this article, more general considerations will now be discussed.

Expansion and shift of SM1 activation after a motor system lesion, either cortical or subcortical, may reflect the “unmasking” or disinhibition by the lesion of preexisting but normally inactive (“latent”) representations; such a built-in overlap of motor representations would therefore represent intrinsic redundancy. As an alternative explanation, these observations may represent “recruitment” of neurons/connections not normally devoted to this function (ie, vicariance), a wholly different type of plasticity of the adult brain^{11,12,21,48} possibly resulting from repair mechanisms such as axonal sprouting with formation of new synapses (see Reference 48 for a review of neurobiological aspects of plasticity) or reflecting normal use-dependent neural plasticity. Both of these hypotheses are supported by electrophysiological and immunohistochemical animal studies. Studies in the rat have demonstrated both enhanced long-term potentiation in areas surrounding the lesion as well as in the contralateral hemisphere early after stroke⁴⁹ and sprouting of fibers and formation of new synapses from the surviving neurons after a few weeks.⁵⁰ However, there is as yet no evidence that displacement/extension of SM1 activation is beneficial to recovery of function, and therefore the clinical significance of this finding is still unclear. Finally, whether or not dynamic changes occur remains unclear.^{33a}

The overactivation of the ipsilesional motor cortex observed after subcortical stroke might reflect an excessive recruitment of this cortical field in an attempt to perform the task despite CST damage (see Figure 4 for a general model). Thus, recovery would be optimal when M1 is not only preserved structurally, as after subcortical as opposed to cortical stroke, but is also capable of enhanced workload, ie, is not completely disconnected. Supporting evidence comes from TMS studies showing that the motor evoked potential amplitude after stimulation of the ipsilesional cortex corre-

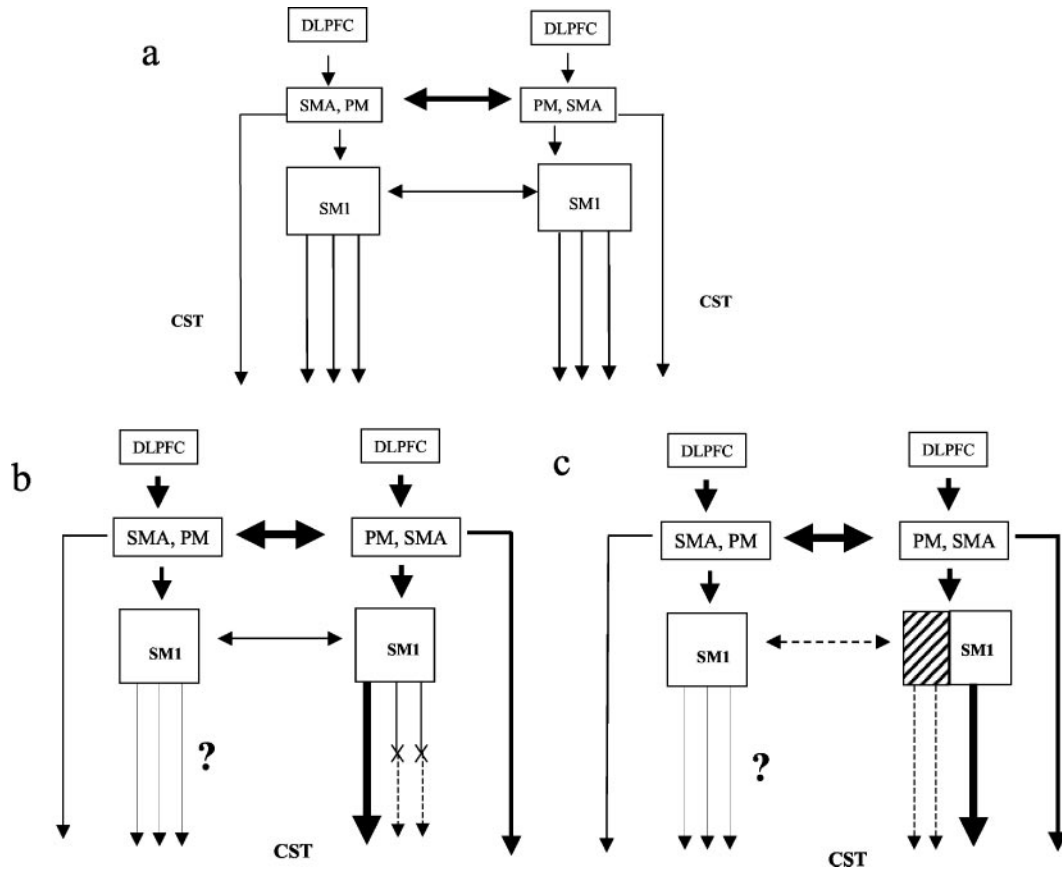


Figure 4. Putative model for functional alterations in motor networks induced by adult stroke partially destroying the CST. This model does not account for all the (sometimes discrepant) observations and does not incorporate the still preliminary information about the dynamics of the changes. In a, a simplified physiological connection model among SM1, SMA, PM, and DLPFC of both hemispheres is shown. In b and c, functional alterations in subcortical and cortical stroke, respectively, are illustrated, with dotted arrows representing interrupted or hypofunctional connection and thicker arrows representing hyperactive connections. Briefly, in subcortical stroke partially destroying the CST (crosses in b), increased firing from structures upstream of the SM1 results in increased activity of the SM1 as well as of the contingent of CST fibers that originate from them, and also entrains their homologue areas of the contralesional hemisphere. A very similar pattern of changes would result from cortical lesions partially destroying the SM1 (hatched area in c), apart from an increased activity of the remaining perinfarct SM1 cortex, and reduced inhibitory output from the lesioned SM1 to the contralesional SM1, possibly contributing to the hyperexcitability of the latter. This model would account for the better motor function associated with activation patterns closer to physiological patterns. Note that this model does not incorporate the uncrossed CST, the cerebellum, or the role of neurotransmitters. The question mark near the contralesional CST reflects the still unclear physiological state and role in motor recovery of this pathway after stroke (see Discussion).

lates with the extent of hand motor recovery.^{51,52} Unmasking of previously silent synapses as well as enhanced input from neighboring PM and SMA would implement this overrecruitment of the affected-side M1 (Figure 4). An alternative hypothesis posits that M1 overactivation reflects simple disinhibition that has no relationship to actual motor performance and recovery.²⁷

Besides this compliance of affected-hemisphere M1, another robust but still incompletely understood finding concerns the recruitment of unaffected-side M1. Some argue that it may merely reflect the occurrence of mirror movements, while others consider that it represents recruitment of the direct (uncrossed) CST to compensate for damage of the ipsilesional (crossed) CST (both hypotheses are not mutually exclusive). Although a weak relationship with mirror movements is apparent across patients, this clearly is not a one-to-one situation. In agreement with TMS studies,^{52–55} functional neuroimaging^{22,30} strongly suggests that, contrary

to widespread expectations, contralesional SM1 activation seems less efficient than ipsilesional activation for adult stroke recovery. Accordingly, Mima et al,⁵⁶ studying the functional connection between motor cortex and muscle by means of electroencephalographic-electromyographic coherence, demonstrated that all direct functional connections to muscle after recovered subcortical stroke come from the contralateral motor cortex. Furthermore, the uncrossed CST has only marginal physiological function, as shown by TMS studies in normal subjects^{52,57} in whom responses in ipsilateral distal upper limb muscles are rarely observed and proximal responses are seen only with intense stimuli.⁵⁸ Taken together, these observations would militate against the implication of the uncrossed CST in recovery of hand function in the adult, although a role in the early recovery of proximal limb function is possible. A different hypothesis to explain these contralesional activations takes into account the fact that studies in healthy subjects have reported activation

of the ipsilateral SM1 during complex as well as nondominant hand motor tasks, pointing to some sort of bihemispheric cooperation. Thus, after a stroke affecting the CST, execution of even the simplest motor task may require recruiting this bilateral network that is normally engaged with complex tasks only. In other words, the recovering brain would process a “simple” motor task as “difficult,” representing a kind of procedural adaptation making use of available resources (redundancy). In case of cortical stroke, activation of the unaffected-side SM1 may originate in part from reduced transcallosal inhibition from the lesioned SM1, while in both cortical and subcortical stroke it would result principally from increased drive from overactive affected-side PM and SMA (Figure 4). Accordingly, contralateral synkinesia would be a consequence, rather than the cause, of unaffected-hemisphere SM1 activation. Longitudinal studies assessing the specific clinical correlation of contralesional activation may provide better understanding of these mechanisms. In one scenario from the few longitudinal studies published to date, contralesional activation might be useful in the acute/subacute stage, but its relative contribution would decline as recovery proceeds.^{21,28} It is, however, possible, and even likely, that the role of unaffected SM1 activation differs in some way between subcortical and cortical strokes,⁵⁹ and this key point will need further investigation. Finally, age at onset of stroke is a key factor with respect to contralesional SM1 activation,⁶⁰ which plays a major role in recovery after childhood-onset stroke.

In addition to overactivation of the ipsilesional SM1, a widespread bilateral recruitment of the secondary motor areas, such as PM and SMA, also occurs after both cortical and subcortical strokes. In normal subjects, these areas are already involved in simple motor functions, but they are more activated during complex tasks. Thus, as already speculated with respect to the contralesional SM1, bilateral overactivation of these areas may reflect excess recruitment of a preexisting large-scale distributed motor network rather than genuine reorganization. One function of such overrecruitment, at least in the affected hemisphere, would be to drive the partially de-efferented or destroyed SM1 into sending sufficient signal to the secondary motor neuron. Accordingly, the amount of overactivation of these areas tends to decline as recovery takes place, even though the task is unchanged,^{17,21} ie, less “effort” is required by the brain to achieve the same workload as reorganization advances. In regard to the PM in particular, however, both cross-sectional¹⁵ and longitudinal studies^{17,21} suggest that this area (especially contralesional) becomes overactivated at the late stage of recovery, indicating redistribution of workload with recovery. Although correlations between recovery and the amount of activation in the PM or other secondary areas have not been reported as yet, it is likely that these areas are of some importance for the restoration of motor functions.⁶¹ It is known that the PM contains corticospinal neurons giving rise to the bilaterally organized cortico-reticulospinal tract^{62,63} and is particularly involved with proximal movement, and therefore it is considered a good candidate for subserving substitution of motor hand function after damage of the motor cortex sparing the

greater part of the internal capsule.^{17,21} The SMA and cingulate motor area also contribute fibers to the CST.

Another interesting finding concerns the recruitment of areas normally not engaged in the execution of a motor task—unless the latter has particular complexity (eg, complex sequencing) or nonmotor components—such as the prefrontal, posterior parietal, and anterior cingulate cortices and the insula. Their involvement after stroke might reflect the bringing into play of compensatory cognitive strategies, eg, visuospatial strategies, to perform the task, however “simple” it may appear to the external observer. The lesser recruitment over time of some of these areas such as the insula and parietal cortex²¹ suggests that recourse to such strategies becomes less necessary as motor recovery proceeds. The bilateral activation of BA 40 during some tasks in normal subjects has been related to transcallosal connections, which may therefore become engaged after stroke. In regard to the occurrence of prefrontal activation in the late phase of recovery,^{10,15,21} it may reflect a late compensatory mechanism relaying early motor network recruitment. Also overactivated after stroke is the basal ganglia,²¹ whose physiological role in motor control remains uncertain, although they appear to be particularly involved during motor skill learning. Of interest was the observation of putaminal overactivation in 2 patients who also showed prefrontal overactivation.²¹ Because the prefronto-striatal loop is physiologically activated when a subject learns a new motor task or pays extra attention to the performance of a prelearned task,⁴⁵ these cognitive processes might be engaged as compensatory implicit strategies after stroke. Since essentially all the aforementioned observations have been made in patients with subcortical stroke, it is unknown whether the same mechanisms apply to cortical stroke, and to date no longitudinal study specifically assessing cortical stroke has been reported.

As a simple index of interhemispheric functional balance, the LI has recently attracted considerable interest. Although across the studies the calculation of LI refers to absolute numbers of significantly activated voxels based on different levels of significance, the findings have shown remarkably similar characteristics (Figure 2). Although the LI is of considerable interest because it represents the balance of activation between the affected and unaffected hemispheres, it gives no information about the actual level of ipsilesional or contralesional activation itself or about the actual level of significance in the activated clusters. Recently, a more “weighted” LI calculation has been introduced by Fernandez et al⁶⁴ in a study of language; application in motor recovery after stroke would be worthwhile. As illustrated in Figure 2, in both cross-sectional and longitudinal studies, a major feature has been the broader distribution of LI values in patients at the chronic stage of recovery compared with controls because of the frequent occurrence of prominent (and occasionally predominant) contralesional activation. A better recovery seems to take place if the changes in LI over time are such that the normal balance between the 2 hemispheres tends to reestablish.²² These findings concur with several descriptive reports about aphasia (both cross-sectional^{65,66} and longitudinal⁶⁷) or neglect,⁶⁸ which consistently suggested that recovery is best when the brain regions

that normally execute the function are reintegrated into the active network. According to this concept, contralesional SM1 activation may represent maladaptive plasticity, possibly resulting from disuse or “learned non-use”⁶⁹ of the affected-side remaining potential or unconscious lack of “effort.”

Consistent with this hypothesis, intense rehabilitative procedures (both active and passive) as well as specific pharmacological manipulations have recently been shown to enhance activation of the ipsilesional SM1,^{20,24,26} in parallel with improved motor function in 2 rigorous studies.^{24,26} These findings are entirely consistent with a TMS study on constraint-induced therapy that showed greater area of SM1 excitability after training.^{36,46} These studies therefore suggest that it is possible to manipulate plasticity in the lesioned adult brain in the same way as achievable in the normal brain⁷⁰ to entrain or “force” the brain with maladaptive plasticity toward a more physiological, and hence more efficient, activation pattern. Learned non-use of the upper extremities appears to be overcome by constraint-induced therapy.⁶⁹ Interestingly, the fact that passive movements seem to have similar use-dependent effects on the ipsilesional SM1²⁰ suggests that applying passive therapy in the acute stage, ie, when patients cannot move the affected limbs, may also improve outcome. Equally important is the observation that it is possible to nearly renormalize brain organization in the chronic phase of stroke²⁶ because this opens new perspectives for the chronically disabled. Although they are of interest and open new perspectives for therapeutic interventions, these findings should not be confounded with adequately powered clinical trials.

General Issues

Although work performed thus far has focused primarily on the role of the cerebral cortex and cerebellum in plasticity, important reorganization may also involve the basal ganglia, thalamus, and spinal cord when their role in normal motor function is considered. For technical reasons, functional imaging techniques have until now not been optimal for the study of these structures.

Disentangling the role in recovery of each component of the motor network versus the entire circuit can be achieved in principle by functional imaging, as follows: (1) by assessing the correlation between recovery on one hand and activation in each component or in the modeled network on the other hand (using, eg, structural equation modeling),⁷¹ and (2) by guiding TMS (single or repetitive) to stimulate or inhibit each cortical area separately.⁶¹ In doing so, it will be important to perform longitudinal assessments because the role of a given area in recovery may conceivably change as time elapses.

The fine behavioral correlates of activation pattern changes after stroke have not been addressed thus far. For instance, quantitative assessment of the actual movement produced during scanning, such as speed, accuracy, amplitude, and pacing, should be obtainable with the use of recording devices such as accelerometry.⁷² In addition, comparing simple motor tasks with more elaborate paradigms involving, eg, explicit or implicit learning, reaching, action observation, and movement imagination, might shed light on the implica-

tion of compensatory cognitive strategies in the activation of nonmotor areas such as the dorsolateral prefrontal cortex (DLPFC) in chronic stroke. The role of “effort” and motivation may also influence the activation pattern. Within the somatosensory system itself, the involvement of sensory input (especially proprioceptive) in motor reorganization, suggested by, eg, posterior displacement of SM1 peak activation,²³ may prove important in the recovery process.

The issue of individual variability, as well as the influence of age,⁷³ sex, handedness, and possibly premorbid behavioral profile, needs to be investigated. Exact location and size of the lesion should be considered, and more specifically the amount of CST damage,^{27,74} which can be assessed with structural and diffusion tensor MRI and also by measuring the *N*-acetyl-L-aspartate content with MR spectroscopy and by TMS.

To achieve a better understanding of the neurobiological and neurophysiological mechanisms underlying the changes in brain activation pattern after stroke, including the precise temporal course of activation within each component of the motor network before and after movement execution, it will be important to combine functional imaging both with high temporal resolution brain mapping techniques such as electroencephalography and magnetoencephalography and with TMS, which can assess intracortical inhibition and facilitation^{75,76} as well as modulation of function in reorganized brain regions.^{61,77–79} Neurotransmitters such as GABA, the most important inhibitory neurotransmitter in the brain, can now be assessed with MR spectroscopy. This is important because modulation of GABAergic inhibition plays a significant role in cortical plasticity by unmasking of latent synapses.⁸⁰

It has long been established that focal stroke may induce widespread reductions in resting CBF and glucose and oxygen metabolism (so-called diaschisis),^{81,82} and there is a trend for neocortical diaschisis to improve over time in parallel with recovery, which would represent another manifestation of plasticity.⁸³ It would therefore be important to investigate whether, and if so how, the 2 phenomena interact, ie, if they have synergistic, independent, or antagonistic effects on recovery. This issue has received little attention thus far.^{10,21,84} Likewise, survival of the penumbra is a major determinant of midterm recovery after ischemic stroke,^{85,86} and it has been suggested that survival of the penumbra may offer opportunities for peri-infarct reorganization; this idea would be consistent with the aforementioned findings in partial SM1 infarcts.^{12,14} However, the actual relationships between ultimately surviving penumbra and subsequent infarct rim activation have not been studied.

A wide-open field of research regards the effects of rehabilitation and training on brain plasticity as assessed by functional imaging. Although a few recent studies showing “recruitment” of the SM1 cortex by training in chronic subcortical stroke suggest huge opportunities,^{20,26} further investigations are needed not only to confirm their findings but also to assess whether the benefits from a period of training are retained and whether repeating the training period reproduces its initial effects. In addition, how early after stroke reorganization starts and how early this can be manipulated by rehabilitation remain unknown. In regard to poorly

recovered patients with partial lesions of the SM1, whether rehabilitation can use-dependently drive peri-infarct activation in parallel with improved function, as appears to occur in monkeys,⁸⁷ needs to be tested. The same comments apply to the effects of medication, of which only acute single-dose effects have been studied thus far.²⁴ Finally, recent studies suggest the possibility of manipulating plasticity with repetitive TMS.⁷⁹

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