Contribution of the Ipsilateral Motor Cortex to Recovery after Chronic Stroke

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It has been proposed that the intact (ipsilateral) motor cortex play a significant role mediating recovery of motor function in the paretic hand of chronic stroke patients, but this hypothesis has not been tested experimentally. Here, we evaluated the effects of transcranial magnetic stimulation (TMS) on motor performance of the paretic hand of chronic stroke patients and healthy controls. We hypothesized that, if activity in the intact hemisphere contributes to functional recovery, TMS should result in abnormal motor behavior in the paretic hand. We found that stimulation of the intact hemisphere resulted in delayed simple reaction times (RTs) in the contralateral healthy but not in the ipsilateral paretic hand, whereas stimulation of the lesioned hemisphere led to a marked delay in RT in the contralateral paretic hand but not in the ipsilateral healthy hand. RT delays in the paretic hand correlated well with functional recovery. Finger tapping in the paretic hand was affected by TMS of the lesioned but not the intact hemisphere. These results are consistent with the idea that recovered motor function in the paretic hand of chronic stroke patients relies predominantly on reorganized activity within motor areas of the affected hemisphere.

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The substrates mediating recovery of motor function after stroke are incompletely understood.[1] Previous reports identified activation of the intact (ipsilateral) motor cortex in association with recovery of motor function in the paretic hand.[2–4] Based on this evidence, it has been postulated that activity in this region plays a crucial role mediating functional recovery.[5,6] However, several caveats make this proposal questionable. First, the magnitude of activation (functional magnetic resonance imaging [MRI] or positron emission tomography) of the intact motor cortex with movements of the paretic hand does not correlate with functional recovery.[5] Second, mirror movements in the intact hand when intending to move only the paretic hand contaminated some previous neuroimaging studies.[3,7] Third, ipsilateral corticomotoneuronal connections from the intact hemisphere to the paretic hand are functionally most effective in individuals who experience poor motor recovery.[8,9] Therefore, it remains to be determined if activity in the intact motor cortex contributes directly to recovery of motor function after chronic stroke.

In this study, we intended to explore this hypothesis in a cross-sectional study of chronic stroke patients with different degrees of motor recovery. The overall approach was to evaluate the consequence of a "virtual lesion" of cortical areas mediating motor outflow originated in the intact hemisphere on motor performance in the paretic hand. Deteriorated motor behavior of the paretic hand resulting from this intervention would be interpreted as direct evidence for its functional relevance as a substrate of motor recovery.

Subjects and Methods

Subjects

Twenty patients with single ischemic cerebral infarcts aged 61.5 ± 13.6 (SD) years (six women, all but two were right-handed) and 10 healthy volunteers aged 54.9 ± 6.9 years (four women, all right-handed) participated in the studies. All participants gave their written informed consent to each experiment according to the declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm), and the National Institute of Neurological Disorders and Stroke Institutional Review Board approved the study protocol.

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Patient Inclusion Criteria

Patients had a single ischemic cerebral infarct leading initially to complete paralysis (13 left and 7 right hemiparesis). They were tested at least 1 year after a stroke that was followed by different degrees of motor recovery (Table; Fig 1). At the time of the study, patients were 6.2 ± 2.7 (range, 2–11) years poststroke. All patients had visual perception within normal limits and a normal Mini-Mental State Examination score. Average muscle strength in hand and forearm muscles on the paretic side was 3.6 ± 4.0 (n = 16; range, 1–4+ on the Medical Council Research scale). Fugl-Meyer scale (upper extremity section)[10] was 66.3 ± 23.1% for the whole arm and 60.5 ± 31.6% in the hand (n = 17).

Magnetic Resonance Imaging and Volumetric Measures

In 15 patients T1-weighted MRIs were obtained from General Electric Signa scanners (Milwaukee, WI). Images were analyzed on a LINUX workstation using MEDx (Sensor Systems Sterling, VA) to calculate lesion volumes. Sketches of lesion sites were drawn using Adobe Illustrator and Photoshop (see Fig 1).

Experiment 1 (Effect of Transcranial Magnetic Stimulation on Reaction Times in Patients with Good Recovery)

Eight patients (Patients 1, 4–6, 9, 10, 13, 14 in the Table) were instructed to perform index finger flexion movements in response to a GO signal. Each patient's arm was immobilized on a table with the hand reaching a response pad (RB-420; Cedrus Corporation, San Pedro, CA). The pad was linked to a laboratory computer to record the timing of key presses (software: Presentation, Neurobehavioral Systems, San Francisco, CA). After training (2 blocks of 36 trials each), subjects had to press a response key as quickly as possible in response to a randomly displayed GO signal preceded by a warning signal. Electromyogram (EMG) recordings were obtained bilaterally from first dorsal interosseous (FDI) and finger flexors (FF) muscles. Transcranial magnetic stimulation (TMS) was delivered 100 milliseconds after the GO signal at 130% of resting motor threshold (rMT) intensity to the optimal scalp position (OSP) to elicit motor-evoked potential (MEP) in the contralateral FDI muscle. The order of right, left, and sham stimulation as well as the right-left responding hand was pseudorandomized and counterbalanced across subjects. In the sham condition, a second

Table. Clinical Characteristics of Stroke Patients

Patient No.	Age (yr)	Sex	Duration (yr)	Side Affected[a]	MRC[b]	Fugl-Meyer[c]	iMEPs	Lesion Site
1[d]	64	M	8.4	R	4.8	nd	nd	L internal capsule, basal ganglia
2	72	M	7.8	R	4.7	88%	−	R parietal
3	60	F	9.7	L	4.5	83%	+	R internal capsule, basal ganglia
4	58	M	3.4	R	4.4	79%	+	L internal capsule, basal ganglia
5	73	M	3.8	L	4.4	94%	−	R centrum semioval
6	65	M	8	**R**	4.3	83%	-	L internal capsule
7	83	M	9.6	L	4.1	65%	−	R basal ganglia, thalamus
8	45	M	6	L	4.0	89%	−	R MCA territory, R basal ganglia
9	74	F	11.3	**R**	4.0	85%	+	L internal capsule
10[d]	59	M	6.1	L	4.0	nd	nd	R pons
11	53	F	5.5	L	3.9	76%	+	R MCA territory (cortical)
12	58	F	2	**R**	3.8	82%	+	L anterior MCA territory (cortical)
13[d]	73	M	2.1	L	3.8	nd	nd	R anterior pons
14	54	M	8.4	**R**	3.5	67%	−	L MCA territory (cortical)
15	21	M	3.1	L	3.4	74%	+	L occipital-parietal/temporal
16	71	M	3.6	L	2.9	36%	−	R internal capsule
17	45	M	5.7	L	2.8	36%	+	R internal capsule, basal ganglia
18	65	F	4.2	L	2.3	36%	+	R basal ganglia
19	59	F	9.5	R	2.1	27%	+	L frontal operculum, L internal capsule
20	77	M	6.4	L	1.2	26%	+	R internal capsule

[a]Boldface letters specify hand dominance.
[b]Median of 16 muscles.
[c]Percentage of maximum points in upper limb section.
[d]Participated only in experiment 1.

MEP = ipsilateral motor-evoked potential; R = right; L = left; nd = not done.

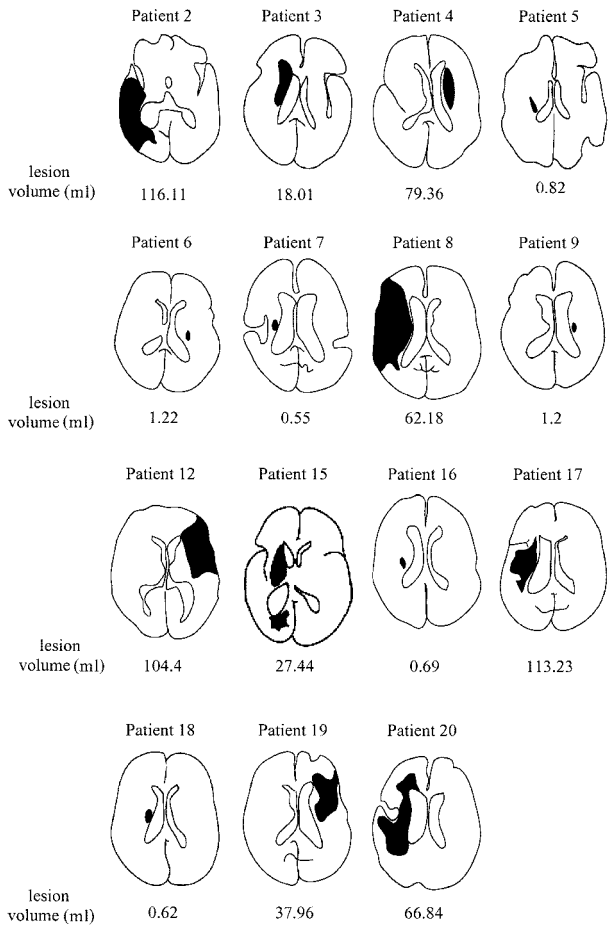

Fig 1. Schematic representation of magnetic resonance imaging lesion sites and volumes. Patient numbers correspond with those in the Table.

coil was held tangentially to the subject's head, with the lower loop touching the skin at the vertex. A total of 144 TMS and 144 sham trials were collected in each subject (8 blocks of 36 trials, 2 blocks per hemisphere/hand combination). Reaction time (RT) was defined as the time interval between the GO signal and the onset of the EMG burst (defined as the time when the EMG amplitude exceeded by 3 SD the EMG activity in the 100 milliseconds preceding the GO signal). Trials in which RT exceeded 3 SD of all trials within one block and condition were excluded from the analysis.

Experiment 2 (Effect of Transcranial Magnetic Stimulation during Motor Activity in Patients with Good Recovery)

Five patients participated in this study (Patients 1, 3, 6, 10, 13 in the Table). Subjects were blindfolded and seated in front of an electronic keyboard (Yamaha pf85; Yamaha, Hamamatsu Shizuoka, Japan). Their forearms were immobilized in splints that allowed only key-press movements. In each 10-second trial, patients were instructed to press a key on the electronic keyboard as quickly as possible. The keyboard was connected to a laboratory computer via MIDI interface (MIDI translator; Opcode Systems, Palo Alto, CA). Special software (Vision 1.4, Opcode Systems) was used to record timing and kinematic information of key presses for further analysis. TMS was delivered to the right OSP, left OSP, and to the vertex for 5 seconds in 10 trials for each spot at 1Hz using an intensity of 150% of rMT of the stimulated hemisphere. The order of the site of stimulation and responding hand was pseudorandomized and counterbalanced across subjects. We measured tapping speed (Hz), duration (in milliseconds) and variability of tapping intervals (expressed as a coefficient of variance of the tapping interval), and tapping force exerted on the piano key (expressed on an arbitrary, ordinal scale with values ranging from 0 to 127).

Experiment 3 (Effect of Downregulation of Motor Activity in Intact Hemisphere on Motor Performance)

In this experiment, performed on five patients (Patients 1, 5, 6, 10, 13 in the Table), 1Hz TMS stimulation was applied for 30 minutes with an intensity of 150% of rMT to the OSP in the intact hemisphere. Downregulation of motor excitability outlasts the period of stimulation by approximately 10 minutes.[11] The order of the two stimulation conditions (sham or ipsilateral OSP) was counterbalanced between subjects. Ten sequences were recorded after each stimulus mode.

Experiment 4 (Effect of Transcranial Magnetic Stimulation on Reaction Time in Patients with Good and Poor Recovery)

Seventeen subjects participated in a RT experiment identical to experiment 1 except that the required responses to the GO signal were wrist flexion movements (recording from FF muscles) to allow patients with poor recovery to participate. Subjects were stratified in two groups: those with poor (median MRC score, <4; n = 9) and good (median MRC score, ≥ 4; n = 8) motor recovery (see Table).

Recording and Stimulation Procedures

EMG (50–2kHz) was recorded from silver-silver-chloride electrodes positioned in a belly-tendon montage on the skin overlying the target muscles and the signal was digitized (sampling rate, 5kHz) for off-line analysis (Counterpoint Electromyograph; Dantec Electronics, Skovlunde, Denmark). For TMS, we used a Magstim 200 (Magstim, Whitland, Dyfed, UK) stimulator connected to a figure eight (outer loop diameter, 9cm) magnetic coil placed perpendicular to the direction of the central sulcus, approximately 45 degrees to the midsagittal line. rMT was measured at the OSP for the FDI or FF and was defined as the minimal stimulus intensity that produced MEPs greater than 50μV peak-to-peak in amplitude in at least 5 of 10 trials. In 17 patients and 10 controls, we tried to detect ipsilateral MEPs (iMEPs) during mild voluntary contraction (15–25% of maximum voluntary contraction) of the target muscle by collecting 20 trials applied at 0.1Hz with a stimulus intensity of 100% stimulator output over each OSP. IMEPs were identified by visual inspection in averaged EMG traces as EMG potentials that clearly exceeded EMG background activity (see raw data examples in Fig 2).

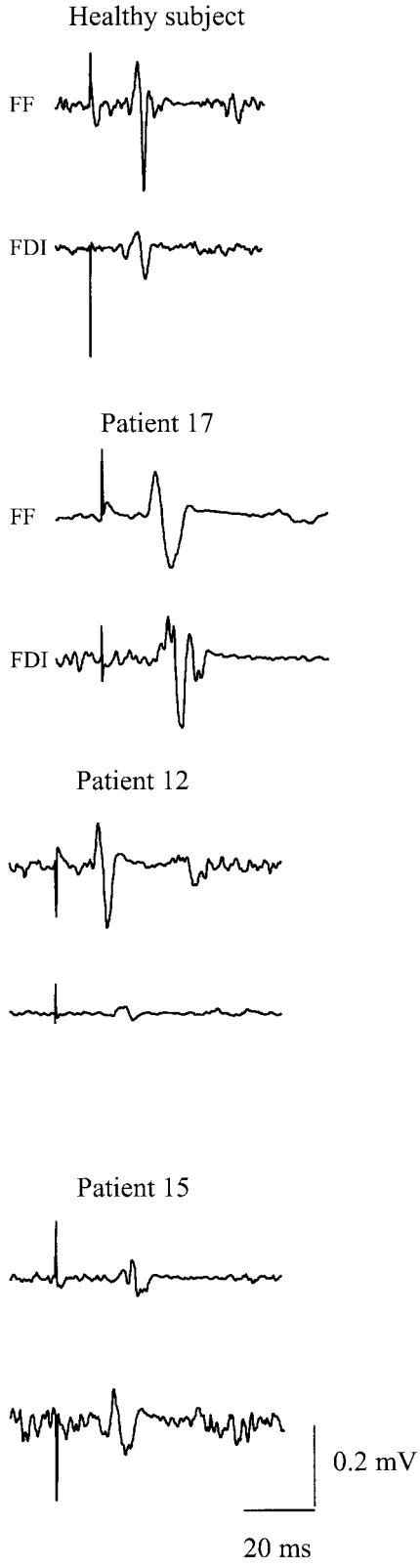

Fig 2. Raw data examples of motor-evoked potentials (as average of 20 trials) when stimulating the ipsilateral motor cortex recorded from, FF (top traces) and FDI (bottom traces) muscles. FF = finger flexors; FDI = first dorsal interosseous.

Statistical Analysis

After testing for normal distribution (Shapiro-Wilk test of normality) and homogeneity of variance (Bartlett's χ^2), we used three-way, repeated-measures analysis of variance (ANOVA) with arm (paretic/healthy), hemisphere (ipsilateral and contralateral to the hand performing the task), and type of stimulation (test/sham) as between-subject variables for the analysis of the RT data. To compare group results in experiment 4, we considered arm, hemisphere, and recovery (poor or good recovery) to be between-subject variables, and RT was expressed relative to the sham condition. In experiment 4, the presence or absence of ipsilateral MEPs (iMEPs), hemisphere, and arm were between-subject variables. Behavioral variables such as tapping speed, duration, variability, and force were averaged within each trial and analyzed separately using repeated-measures ANOVA with the site of stimulation (ipsi-OSP, contra-OSP, vertex, sham, no stimulation) as within-subject variables. Corrected Fisher's Least Significant Difference (protected *t* tests) were applied for post hoc, pair-wise comparisons. We used two-way *t* statistics for normally distributed and Mann–Whitney *U* test for nonparametric data. Frequency counts were compared by calculating Yates-corrected χ^2values. Unless otherwise noted, variance is expressed as the standard error of the mean. Results were considered significant at a level of p value less than 0.05.

Results

Experiment 1

In training trials, RT was longer in the paretic than in the intact hand (210.5 ± 12.7 vs 195.8 ± 10.4 milliseconds; $p = 0.032$). rMT in FDI was significantly higher with stimulation of the lesioned compared with the intact hemisphere (64.7 ± 8.2% vs 43.9 ± 2.2%; $p = 0.02$).

Evaluation of RT measured in FDI and FF muscles showed significant effects of *ARM* ($F = 5.4$; $p < 0.04$), *hemisphere* ($F = 17.1$; $p < 0.001$), and *stimulation* ($F = 23.5$; $p < 0.001$), with significant interactions of *ARM* × *hemisphere* ($F = 4.6$; $p < 0.05$), *hemisphere* × *stimulation* ($F = 25.7$; $p < 0.001$), and *ARM* × *hemisphere* ×*stimulation* ($F = 4.6$; $p < 0.05$). RT in FDI was significantly delayed by stimulation of the contralateral hemisphere (paretic hand; $p < 0.01$; intact hand; $p < 0.05$; Fig 3A). Similarly, RT in FF was significantly delayed by stimulation of the contralateral hemisphere (paretic hand; $p < 0.01$; intact hand; $p < 0.05$). The RT delay elicited by contralateral TMS did not correlate with RT in unstimulated trials. Therefore, patients with long RT in unstimulated trials experienced comparable TMS-induced RT delays as those experienced by patients with shorter RT sin unstimulated trials.

RT did not change with ipsilateral stimulation in either patients or controls (see Fig 3A). RT delay elicited in the paretic hand after stimulation of the lesioned hemisphere was more pronounced than RT delay elicited in the healthy hand after stimulation of the intact

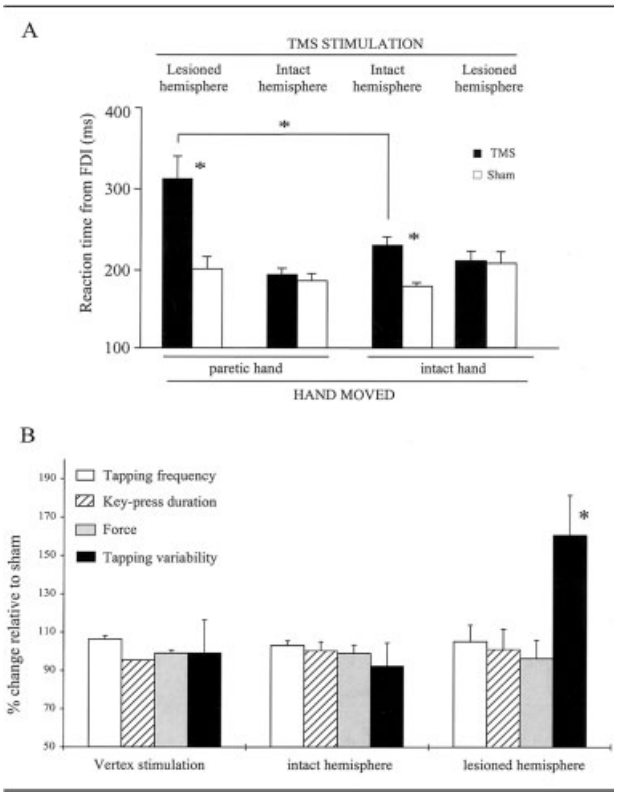

Fig 3. (A) Experiment 1. Mean reaction time (RT) in paretic and intact hands with transcranial magnetic stimulation (TMS) or sham stimulation over the intact or lesioned hemisphere. TMS led to significant RT delays only in the contralateral hands. Note that the delay elicited by stimulation of the lesioned hemisphere in the paretic hand was larger than the delay elicited by stimulation of the intact hemisphere in the intact hand. (B) Experiment 2. Effects of TMS applied to different brain areas on tapping performance in the paretic hand. Note that stimulation of the lesioned hemisphere disrupted significantly tapping variability.

hemisphere ($p < 0.05$ for both FDI and FF; see Fig 3A).

Experiment 2

ANOVA showed a significant effect of stimulation on tapping force ($F = 4.6$; $p < 0.05$) and tapping variability ($F = 3.3$; $p < 0.05$). Specifically, tapping variability in the paretic hand increased with stimulation of the lesioned hemisphere relative to sham (by 60.5 ± 20.9%; $p < 0.05$; see Fig 3B). We detected no further changes in other variables, in particular by ipsilateral stimulation.

Experiment 3

ANOVA showed no significant ($F < 0.5$) effect of 30 minutes of 1Hz TMS on tapping speed, duration and variability, or force between sham and TMS sessions. Tapping speed, duration, and variability during sham stimulation was similar in experiments 2 and 3.

Experiment 4

PATIENTS. Nine patients were assigned to the poor (four women, all right-handed, six with right hemiparesis) and eight were assigned to the good (two women, all but one right-handed, three with right hemiparesis) motor recovery groups (see Subjects and Methods). Age and time interval to the stroke were similar in both groups (age, 54.0 ± 15.3 years vs 66.25 ± 11.1 years; time interval to the stroke, 5.6 + 2.4 vs 7.5 + 2.7 years).

MOTOR THRESHOLDS. rMT in FF was significantly higher with stimulation of the lesioned compared with the intact hemisphere in patients with poor recovery (75.5 ± 10.2% vs 38.5 ± 3.2%; $p < 0.01$), but it was similar in patients with good recovery (48.1 ± 3.9% vs 39.5 ± 1.0%; $p = 0.067$). rMT of the lesioned hemisphere was higher in patients with poor recovery than in those with good recovery (75.5 ± 10.2% vs 48.1 ± 3.9%; $p < 0.05$). In the intact hemisphere, rMT was similar in both groups (38.5 ± 3.2% and 39.5 ± 1.0%, respectively) and did not differ from controls (43.7 ± 3.0%; $p > 0.25$). Lesion volume tended to be larger in the poor recovery group (median, 38.0 ± 16.1ml) compared with the good recovery group (median, 9.6 ± 14.9ml).

REACTION TIME IN TRAINING TRIALS. RT in FF in the paretic arm was longer in patients than in controls (ANOVA, $F_{1,4}$ 7.6; $p < 0.001$). This difference was evident in patients with both good and poor recovery (217.0 ± 11.7 and 244.5 ± 16.0 milliseconds, respectively, vs 173.5 ± 3.2 milliseconds in controls; $p < 0.01$). In the intact arm, RT in patients with good recovery was longer than in controls (210.0 + 8.6 vs 173.5 + 3.2 milliseconds; $p < 0.05$). There was no significant difference of RT in the intact arm between patients with poor recovery and controls (179.0 ± 8.2 vs 173.5 ± 3.2 milliseconds, not significant). Comparison between patients with good or poor recovery using ANOVA with *RECOVERY* and *ARM* as between-subject variables showed a significant effect of ARM ($F_{1,9}$ 8.7; $p < 0.05$) but not *RECOVERY* ($F < 0.1$) with a significant interaction between both factors ($F_{1,9}$ 5.3; $p < 0.05$). Post hoc testing demonstrated longer RT in the paretic compared with the intact arm only in patients with poor recovery (244.5 ± 16.0 vs 179.0 ± 8.2 milliseconds; $p < 0.01$).

REACTION TIME IN TRANSCRANIAL MAGNETIC STIMULATION TRIALS WITHIN PATIENT GROUP. In patients with good recovery (Fig 4), ANOVA showed significant factors *ARM* ($F_{1,8}$, 16.5; $p < 0.01$), *HEMISPHERE* ($F_{1,8}$, 15.5; $p < 0.01$), and STIMULATION ($F_{1,8}$, 79.1; $p < 0.01$) with significant interactions *ARM* × *HEMI-*

SPHERE ($F_{1,8}$ 7.7; $p < 0.01$), *ARM* × *STIMULATION* ($F_{1,8}$ 21.7; $p < 0.001$), and *HEMISPHERE* × *STIMULATION* ($F_{1,8}$, 50.5; $p < 0.001$) as well as interaction between all three factors ($F_{1,8}$, 18.9; $p < 0.001$). Post hoc testing showed significant RT delays in contralateral FF with stimulation of the intact, as well as the lesioned, hemisphere ($p < 0.01$; see Fig 4A). RT delay in the paretic arm with stimulation of the lesioned hemisphere was longer than in the intact arm with stimulation of the intact hemisphere (by 120.6 ± 19.1 vs 36.0 ± 6.4 milliseconds; $p < 0.01$). There was no significant delay on either side with ipsilateral stimulation.

In patients with poor recovery (see Fig 4), ANOVA showed significant factors *ARM* ($F_{1,9}$, 22.4; $p < 0.001$) and *STIMULATION* ($F_{1,9}$, 6.1; $p < 0.02$) with significant interaction *ARM* × *STIMULATION* ($F_{1,9}$, 4.9; $p < 0.05$). RT was significantly delayed and the delay was of a similar degree (by 55.9 ± 35.5 vs 33.1 ± 7.7 milliseconds, not significant; see Fig 4) with stimulation of the contralateral hemisphere in both the paretic as well as in the intact arm.

REACTION TIME IN TRANSCRANIAL MAGNETIC STIMULATION TRIALS ACROSS PATIENT GROUPS. In this analysis, RT in stimulated trials were expressed relative to sham stimulation. ANOVA showed a significant effect of RECOVERY ($F_{1,9}$, 7.2; $p < 0.02$) and ARM ($F_{1,8}$, 49.7; $p < 0.001$), but not HEMISPHERE ($F_{1,9}$, 3.2, not significant), and a significant interaction between all three factors ($F_{1,9}$, 4.8; $p < 0.05$). Post hoc testing demonstrated that RT delays with contralateral stimulation were significantly longer in patients with good recovery than in those with poor recovery (163.3 ± 8.6 vs 118.5 ± 10.7%; $p < 0.01$; see Fig 4). Correlation analysis between recovery and RT delay in the paretic hand indicated that patients with good recovery exhibited longer RT delays with contralateral stimulation ($r = 0.63$; $p < 0.01$; Fig 5). When the RT delay was normalized to the RT without TMS to compensate for individual differences of RT (see discussion below), delays with contralateral stimulation were still significantly longer in patients with good recovery than in those with poor recovery (0.47 ± 0.05 vs 0.85 ± 0.06; $p < 0.01$).

IPSILATERAL MOTOR-EVOKED POTENTIALS. iMEPs were significantly more frequent in patients (10 of 17) than in controls (3 of 10) (χ^2, 15.9; $p < 0.01$). iMEPs were present bilaterally in six patients and unilaterally in four, and they were more frequent on the paretic than on the intact arm (65% vs 47%; χ^2, 5.9; $p < 0.05$) and in patients with poor recovery than in those with good recovery (78% vs 38%; χ^2 31.2; $p < 0.01$; Fig 6). There was no difference in the frequency of iMEPs in patients with good recovery and in controls (χ^2, 1.4, not significant).

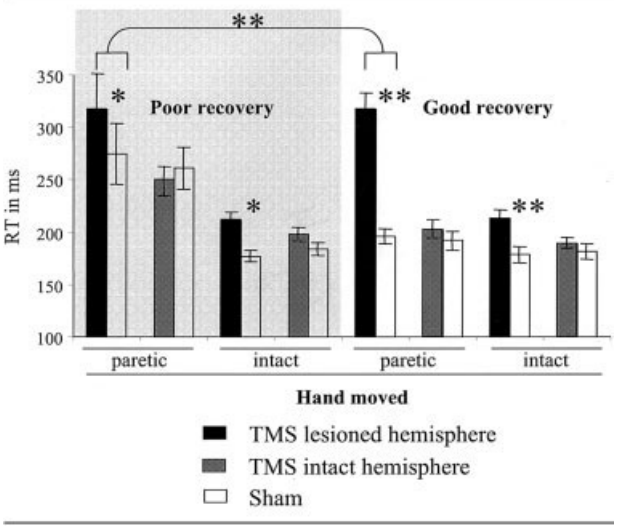

*Fig 4. Experiment 4. Reaction times (RTs) grouped according to the degree of motor recovery (shaded area to left) or presence of ipsilateral motor-evoked potentials (iMEPs) (unshaded area). In the shaded area, filled bars represent trials with transcranial magnetic stimulation (TMS) over the lesioned and dashed bars TMS over the intact hemisphere. In the unshaded area, dashed bars symbolize patients with and open bars those without iMEPs. Note that in both recovery groups, only contralateral TMS stimulation led to significant RT delays compared with sham. The delay elicited by stimulation of the lesioned hemisphere in the paretic hand was more prominent in patients with good recovery than in those with poor recovery (shaded area). **p < 0.01; *p < 0.05.*

Discussion

The purpose of this study was to evaluate the role of the primary motor cortices on the recovered motor function after chronic stroke. Previous neuroimaging and TMS studies raised the hypothesis that enhanced activity in

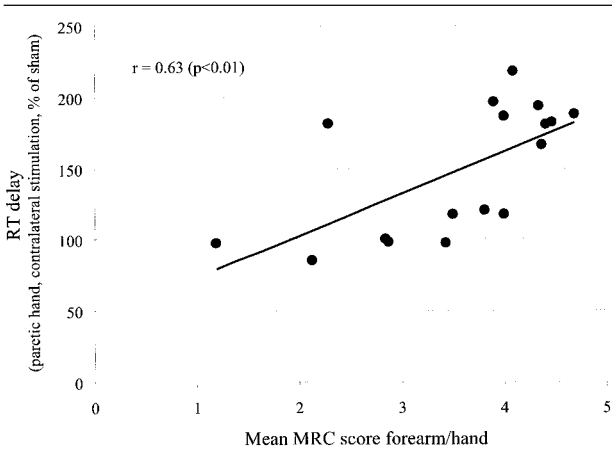

Fig 5. Correlation between the degree of recovery of motor function and reaction time (RT)delay in the paretic hand with transcranial magnetic stimulation (TMS) stimulation of the lesioned hemisphere (n = 17).

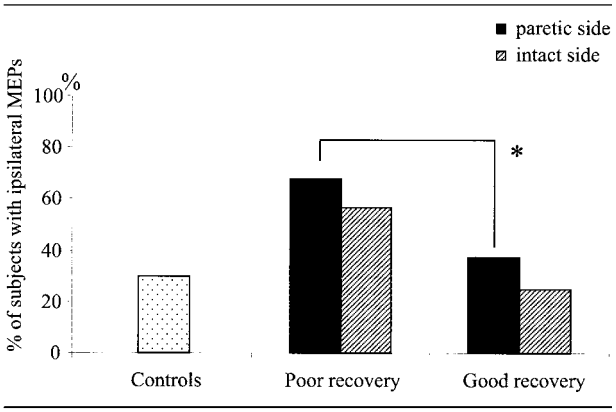

*Fig 6. Percentage of subjects with ipsilateral motor-evoked potential (MEP) in the control group, and in patients with poor or good recovery. Note that the frequency of ipsilateral MEPs is higher in patients with poor recovery (n = 9) than in controls (n = 10) or than in patients with good recovery (n = 8). *p < 0.01.*

the intact motor cortex plays a contributing role in the compensation of motor handicaps resulting from chronic stroke.[2–4,7–9] To address this question, we evaluated a group of stroke patients with variable degrees of motor recovery who had to at least be able to generate a measurable EMG burst from wrist flexor muscles in response to a GO signal. Evaluation of MRI data showed a trend for lesion volumes to be higher in patients with poor recovery than in those with good recovery.

Eliciting a "Transient, Virtual, Reversible Lesion"

We studied the behavioral consequences of eliciting a "transient, virtual, reversible lesion" using TMS in a well-established approach in two different ways.[12–14]

First, in the RT experiments we applied single-pulse TMS to the target cortical sites at a fixed time interval of 100 milliseconds after the GO signal. In healthy volunteers, this technique leads to a delay in RT in the contralateral but not the ipsilateral hand in the absence of changes in the characteristic triphasic agonist-antagonist-agonist EMG burst configuration.[12,15,16] Hence, TMS temporarily delays the execution but does not distort the motor command stored in strategically placed neurons within the primary motor cortex.[16] This delay has been interpreted as the reflection of a transient disruption, elicited by TMS, in activity in the primary motor cortex, the neural substrate underlying the motor response.[16] Therefore, delays in RT in the paretic hand resulting from the application of TMS to the motor cortex of the intact hemisphere would be interpreted as evidence of its previous participation in recovery of motor function. In addition to RT testing, we evaluated the subjects' performance of repetitive key presses for intervals of 10 seconds. TMS was applied during (for 5 seconds, experiment 2) and preceding (experiment 3) task performance. Second, application of 1Hz TMS for 30 minutes at 50% above rMT, as implemented in experiment 3, leads to transient and reversible downregulation of cortical activity in the underlying cortical structures that outlasts the stimulation period for several minutes.[11] We took advantage of this property of the TMS paradigm to test performance of the motor sequence after the TMS stimulation period ended.

Effects of Transcranial Magnetic Stimulation on Reaction Time

In the absence of TMS during training trials, RT in the paretic hand of patients were longer than in the intact hand of both patients and controls, consistent with previous reports.[17]

For patients with good recovery, the RT delay elicited in the paretic hand by stimulation of the affected hemisphere was more pronounced than that elicited in the intact hand by stimulation of the intact hemisphere. This finding suggests that motor performance relies predominantly on activity in the contralateral (affected) executive motor regions. This view is consistent with our finding that stimulation of the intact hemisphere failed to elicit RT delays (experiment 1) or to disrupt motor performance (experiments 2 and 3) in the paretic hand, whereas stimulation of the lesioned hemisphere resulted in significant increases in tapping variability in the paretic hand (see Fig 3).

Although these results were categorical, it is conceivable that the intact motor cortex may play a different role in patients with different degree of motor recovery or in the acute period after stroke. Interestingly, comparison of patients with good or poor recovery showed that RT delays in the paretic hand after TMS of the affected hemisphere were significantly longer in patients with good than in those with poor motor recovery. Moreover, the more significant recovery the patient sustained, the longer the delay in RT in the paretic hand by stimulation of the affected hemisphere (see Fig 5). These results are consistent with the findings of a recent fMRI study that demonstrated that performance improvements in chronic stroke appear to be linked to increased activation within motor regions of the affected hemisphere.[2] Altogether, these findings strengthen the hypothesis that reorganization of activity in the affected hemisphere underlies the recovery of motor function in chronic stroke patients with good motor recovery.

TMS was delivered at an intensity of 130% of rMT. It could be argued that differences in RT delays elicited by TMS were a consequence of different rMT in the patient groups because RT delays were longer with increasing TMS intensities.[18] However, patients with good recovery and relatively lower rMT, in whom low TMS intensities were applied, registered the longest RT delays. Therefore, the results described cannot be accounted for by differences in rMT across patient groups. Another issue to consider is that TMS was applied at a fixed in-

terval of 100 milliseconds after the GO signal. Because patients with poor recovery showed slightly longer RT than those with good recovery, it could be argued that TMS was applied in these patients closer to the response onset, at a more effective time to induce RT delays.[18] Two findings argue against this possibility. First, analysis of single trials with comparable RT in patients with good and poor recovery showed similar group differences in TMS-induced RT delays. Second, the difference in TMS-induced RT delays across groups greatly exceeded the differences attributed to different timing of application of TMS.[18]

Different mechanisms within the affected hemisphere could contribute to this process, including use-dependent plasticity, recovery from diaschisis, and reorganization in areas adjacent to the lesion site within the affected hemisphere.[19–22] Which structures in the affected hemisphere could sustain the recovered motor function? One possibility would be reorganization in the primary motor cortex, such as that documented after motor training.[23] Alternatively, activity within nonprimary motor regions could contribute to this executive function. For example, whereas the dorsal premotor cortex and SMA have direct corticomotoneuronal connections, the functional role of these connections is incompletely understood in either primates or humans. It is conceivable that these regions within the affected hemisphere may contribute to the recovery of motor function in the paretic hand, as was recently demonstrated in patients with focal strokes involving corticofugal fibers originated in M1 and in primates with focal lesions of the primary motor cortex.[19,24,25]

On the other hand, it is feasible that the intact hemisphere could play a contributing role when reorganized activity in the affected hemisphere is not enough to compensate for the motor deficits. This idea is consistent with the finding of more frequent iMEP in patients with poor motor recovery in this and previous studies.[8,9] It is also supported by evidence of an involvement of ipsilateral motor pathways in motor behavior in patients with hemispherectomy, midline structural abnormalities, congenital mirror movements, and infantile hemiplegia.[26–29] Furthermore, there is anecdotal evidence of patients with good recovery from a previous stroke, in whom hemiplegia reoccurred on the recovered side with a second, pure-motor stroke in the opposite hemisphere.[30] Also, because this is a cross-sectional study, we cannot rule out that the ipsilateral motor cortex is involved early and transiently in recovery, an influence that might have been missed in chronic stroke patients. Moreover, activity in nonprimary motor areas of the intact hemisphere may also contribute to motor recovery in patients with stroke and multiple sclerosis.[31–33] Our study aimed to investigate the role of primary motor cortical regions for the function of the recovered hand. Therefore, we cannot discard the possibility of an involvement of other or neighboring motor areas in recovery. In fact, there is some evidence that the site of ipsilateral motor activity in the primary motor cortex is more anterior and lateral to the spot from which contralateral motor responses can be elicit.[34] Finally, it is conceivable that the recovery of motor function after stroke involves mechanisms that are specific to the site of a lesion and others that are present regardless of the lesion site (such as those evaluated in this study).[19] We hope that understanding these mechanisms will improve our chances to develop rationale strategies to promote recovery of motor function after chronic stroke.

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