Stroke

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Motor Strokes

The Lesion Location Determines Motor Excitability Changes

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Background and Purpose—The purpose of this research was to investigate the impact of lesion location on motor excitability and motor performance.

Methods—We studied patients with pure motor strokes in 4 different brain areas: motor cortex lesions (n=7), striatocapsular lesions (n=13), lacunar lesions of the internal capsule (n=13), and paramedian pontine lesions (n=10). Motor performance tests included the 9-hole-peg test and grip strength recordings. Motor excitability was determined by transcranial magnetic stimulation. Motor thresholds, stimulus-response curves, silent periods, motor cortical inhibition, and facilitation were investigated.

Results—The 4 groups were clinically similar but showed major differences in motor excitability. Only motor cortex lesions had a loss of intracortical inhibition in the affected hemisphere. In the internal capsule lesion group and the pontine lesion group, stimulus-response curves were depressed on the affected side. All of the subcortical lesions showed a prolongation of the silent period in the paretic side. Motor thresholds were predominantly elevated in the lesioned hemisphere of patients with internal capsule or pontine lesions. Motor performance was correlated with silent period duration in internal capsule lesions and with motor thresholds in internal capsule and pontine lesions.

Conclusions—Motor cortex lesions exhibited deficient inhibitory properties. In contrast, subcortical lesions displayed an enhancement of inhibition. Internal capsule and pontine lesions affecting the corticospinal tract on different levels particularly impaired neuronal recruitment. Our results suggest that the lesion location determines a specific pattern of motor excitability changes. (***Stroke***. 2005;36:2648-2653.)

Key Words: cerebral infarction ■ electromagnetics ■ evoked potentials, motor

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Animal experiments have demonstrated that a brain lesion may modify brain excitability not only in the vicinity of the lesion but also in anatomically distant brain areas.[1,2] Investigations in stroke patients have revealed a loss of inhibition in the primary motor cortex in the affected[3–5] and in the nonlesioned hemisphere.[6–8] However, in these studies, the lesion was either large or the patient group was heterogeneous, including cortical and subcortical infarcts with and without sensory impairment or different infarct etiologies. This heterogeneity does not allow us to determine whether a particular circumscript lesion is associated with a characteristic modulation of excitability. Such knowledge would be helpful in order to understand functional brain connectivity and to determine the most relevant electrophysiological parameters for (diagnosis and) prognosis. Therefore, we collected patients with an acute stroke and a well-defined lesion proven by MRI. Patients were separated into 4 groups according to the lesion location. All of the patients had 2 features in common: (1) they presented isolated motor symptoms without involvement of sensory functions or neuropsy-

chological symptoms; and (2) the degree of motor impairment was similar in all 4 of the groups. Thus, we investigated patients with a homogeneous clinical pattern but different lesion locations. A variety of transcranial magnetic stimulation (TMS) techniques were used to examine inhibitory and excitatory phenomena in the central motor system.

Methods

Inclusion criteria were as follows: first ever stroke, onset of symptoms <14 days before the investigation, pure motor symptoms, and degree of strength in the affected upper extremity at 4 (according to the Medical Research Council Scale). The exclusion criteria were as follows: any other neurological or psychiatric illness apart from the stroke, consumption of drugs known to interfere with brain excitability, heart pacemaker, metallic objects in the brain, and pregnancy. The study was approved by the local ethical committee, and patients gave informed consent to participate.

All of the patients underwent neurological examination and MRI scanning. Clinical investigation showed that all of the patients were able to lift the affected arm, bend and extend in the elbow joint, and bend and extend the fingers, corresponding to a degree of strength of 4 on the MRC scale. Sensory testing included touch, pinprick, and

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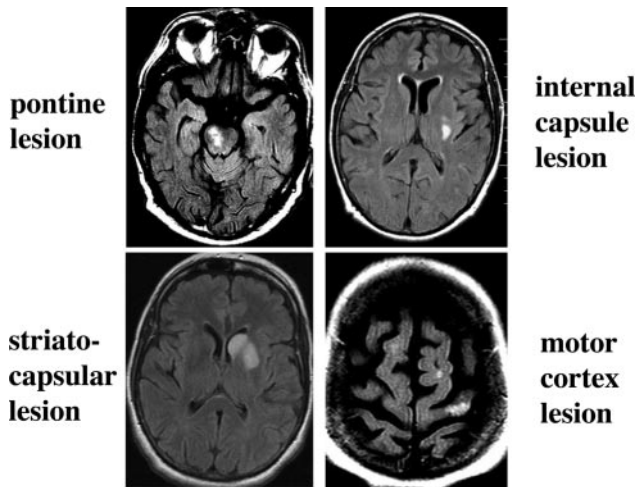
Figure 1. Typical examples of magnetic resonance tomography images (fluid inversion attenuated recovery sequences) of single patients from each group.

vibration. Patients did not have a side-to-side difference in any of these parameters. They were allocated to different groups according to their MRI findings (Figure 1). The following groups were defined as follows: (1) patients with an embolic lesion in the hand knob area of the primary motor cortex (n=7, 2 women, age 73 ± 7 years [mean$\pm$SD], M1 group); (2) patients with an embolic lesion involving the basal ganglia and the internal capsule (SCL group; n=13, 5 women, 63 ± 12 years of age); (3) patients with a lacunar lesion in the internal capsule on the level of the basal ganglia (IC group; n=13, 6 women, 67 ± 12 years of age); and (4) patients with a paramedian pontine infarct (PL group; n=10; 2 women, 71 ± 7 years of age).

TMS

Recordings were taken with surface electrodes (belly-tendon montage) from the first dorsal interosseous muscle bilaterally. The ulnar nerve was stimulated electrically at the wrist with supramaximal intensities to elicit M responses and F waves. TMS was performed with a figure-8 coil (The Magstim Comp.), which was connected to a magnetic stimulator (Magstim 200 HP). To apply paired pulses, the coil was connected to a Bistim device, which triggered 2 magnetic stimulators. The coil was held with the grip pointing posteriorly and perpendicular to the central sulcus. The optimal coil position for primary motor cortex (M1) stimulation was determined by placing the center of the coil 5 cm lateral to the vertex and then moving the coil in steps of 0.5 cm until the position was found where the stimulation produced the largest motor-evoked potentials (MEPs) with the lowest stimulus intensity. This procedure was performed on both hemispheres. Resting motor threshold (MT) was defined as the stimulus intensity needed to produce MEPs with a size of 50 to 100 μV in 5 of 10 consecutive trials during complete muscle relaxation. The silent period (SP) was elicited by single TMS pulses with an intensity of 120% MT during voluntary contraction of the target muscle. Subjects were instructed to activate the muscle with 20% maximum voluntary contraction. The level of contraction was

controlled by auditory feedback through a loudspeaker. Eight trials were recorded, and the mean SP duration was calculated. The SP is thought to be of cortical origin, in particular its later part.[9,10] Intracortical inhibition and facilitation (ICI and ICF, respectively) were examined in a conditioning-test pulse TMS paradigm[11] at complete rest. The first conditioning shock had an intensity of 75% of MT. The intensity of the second pulse was fixed at 120% MT. The following interstimulus intervals (ISIs) were tested: 2, 3, 10, and 15 ms. It has been demonstrated that ICI and ICF are intracortical phenomena.[12,13] Each ISI was tested 8 times and unconditioned test MEPs 24 times in a random order. Stimulus-response curves (SRCs) were tested at rest using single TMS pulses with intensities of 110%, 120%, 130%, 140%, and 150% MT.[14] For each stimulus intensity, 8 trials were performed. In all of the experiments, the time interval between successive stimuli was 5 to 7 seconds.

MEPs were recorded with a sampling rate of 10 kHz. The recordings were filtered (bandpass: 20 Hz to 3 kHz), stored on a Viking IV (Nicolet), and analyzed offline. M responses and MEP amplitudes were measured peak-to-peak.

The SP duration was measured from the onset of the MEP to the reoccurrence of ongoing EMG activity. In the paired-pulse paradigm, conditioned MEP amplitudes were expressed as a percentage of the mean MEP amplitude after single TMS pulses. To increase the power and to obtain a representative mean value for ICI and ICF, we combined conditioned MEP values at ISI of 2/3 ms and 10/15 ms and took the mean conditioned MEP values at 2/3 ms and 10/15 ms as a measure of ICI and ICF, respectively.

Motor Performance Tasks

We used the 9-hole-peg test (9-HPT) to study dexterity.[15] Hand grip strength was also investigated using a mechanical dynamometer (Table).

Statistical Analysis

Because results obtained from the affected side did not follow a normal distribution, we used nonparametric tests for statistical analysis. We examined side-to-side differences within each group and used ratios (affected/unaffected) of SPs, ICI, ICF, and SRCs to compare results between groups. For within-group statistics, we applied either Wilcoxon tests (comparison of MTs, SPs, 9-HPT, and grip strength) or Friedman ANOVA (SRC with different stimulus intensities, intracortical excitability consisting of ICI and ICF). For between-group comparisons, Kruskal-Wallis tests were performed. In case of significant differences, post hoc *t* tests were calculated. In order to correlate electrophysiological results with motor performance, we first calculated ratios (affected/unaffected) for each parameter. Then we applied Spearman rank coefficient for correlation analysis. A significant difference was assumed if $P<0.05$.

Results

Stimulus Response Curves

In the M1 group, a significant difference between the affected and unaffected side was found for the highest stimulus intensity (150% MT; $P=0.046$): MEP amplitudes were smaller on the affected side. The SCL group showed identical SRC on both sides. In the IC and PL groups, MEPs obtained

Motor Excitability Measures and Motor Performance Results in the 4 Patient Groups

Group	MT, % Aff	MT, % Unaff	SP, ms Aff	SP, ms Unaff	9-HPT, s Aff	9-HPT, s Unaff	Grip, lb Aff	Grip, lb Unaff
PL	59 ± 11	45 ± 8	221 ± 50	103 ± 25	109 ± 82	24 ± 4	32 ± 27	67 ± 30
ICL	55 ± 12	44 ± 7	206 ± 53	106 ± 29	84 ± 74	24 ± 4	41 ± 24	69 ± 26
SCL	50 ± 13	45 ± 10	162 ± 60	97 ± 19	60 ± 58	22 ± 5	58 ± 27	68 ± 22
M1L	56 ± 12	46 ± 6	103 ± 45	107 ± 29	49 ± 45	20 ± 2	51 ± 34	86 ± 19

Aff indicates affected side; unaff, unaffected side. Data are given as mean$\pm$SD.
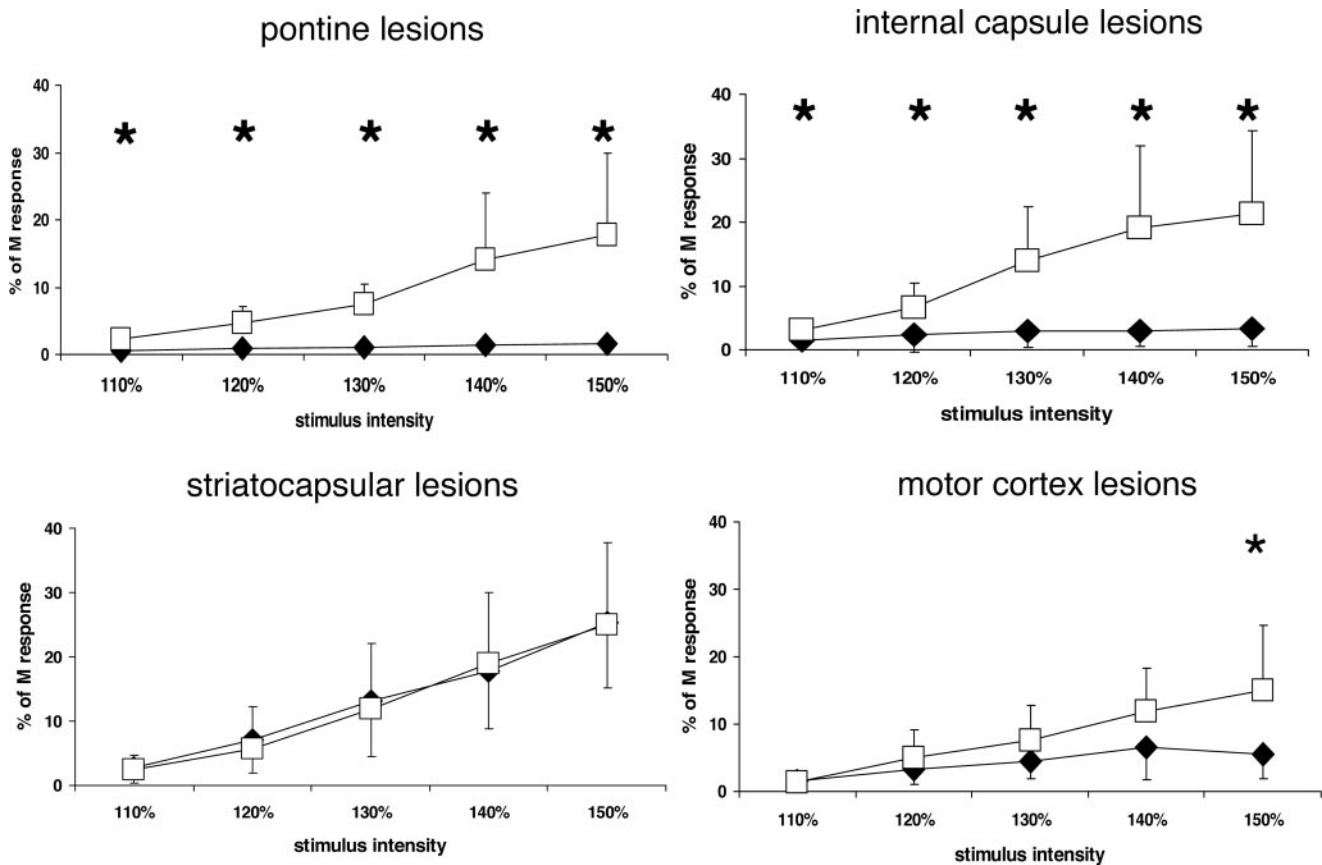
Figure 2. SRCs in the 4 different stroke groups; black symbols represent the affected side, open symbols demonstrate the unaffected side. Vertical axis: MEP amplitudes expressed as percentage of the M response; horizontal axis: stimulus intensity in relation to the individual motor threshold. *$P<0.05$.

from the affected side were significantly smaller than in the unaffected limb (Figure 2). This difference became even more pronounced with higher stimulus intensities. Kruskal-Wallis tests of SRC ratios demonstrated significant differences between the 4 patient groups ($P<0.0001$). Post hoc t tests indicated that significant differences were found between the SCL group and the IC and PL groups.

SPs
In the SCL, IC, and PL groups, the SP was significantly prolonged on the affected side ($P=0.003$, $P=0.002$, and $P=0.008$, respectively). In the M1 group, the SP was non-significantly shorter on the affected side (Table). Kruskal-Wallis tests indicated a significant difference between groups. Post hoc t tests showed that the PL group ($P=0.005$) and the IC group ($P=0.007$) were significantly different from the M1 group.

Intracortical Excitability
There was no side-to-side difference in ICF in any group. ICI was significantly reduced in the affected hemisphere of the M1 group ($P=0.018$) but not in other groups (Figure 3). Kruskal-Wallis tests demonstrated a significant difference in ICI ratios between groups ($P=0.011$). Post hoc t tests showed that ICI ratios in the IC group ($P=0.01$) and the SCL group ($P=0.023$) were significantly smaller than in the M1 group, indicating a more asymmetrical ICI distribution between both

hemispheres in the M1 group. (Table I available online only at http://stroke.ahajournals.org)

MTs
In the PL group ($P=0.019$) and the IC group ($P=0.024$), a significant side-to-side difference was found. MTs in the affected hemisphere were higher than in the healthy hemisphere. A similar trend was found in the SCL group ($P=0.1$) and the M1 group ($P=0.06$; Table). Kruskal-Wallis tests of MT ratios showed no difference between the groups ($P=0.32$).

Motor Performance
9-HPT side-to-side differences were significant in the PL group ($P=0.007$), in the IC group ($P=0.001$), in the SCL group ($P=0.002$), and in the M1 group ($P=0.018$). In each group, performance of the 9-HPT was slower with the paretic hand. According to Kruskal-Wallis tests, the 9-HPT ratios of the 4 groups were not significantly different from each other. Significant grip strength differences between the affected and nonaffected hand were found in the PL group ($P=0.007$), in the IC group ($P=0.002$), in the SCL group ($P=0.002$), and in the M1 group ($P=0.028$). In each group, the affected hand displayed less strength. The between-group analysis of grip strength ratios indicated no significant difference.
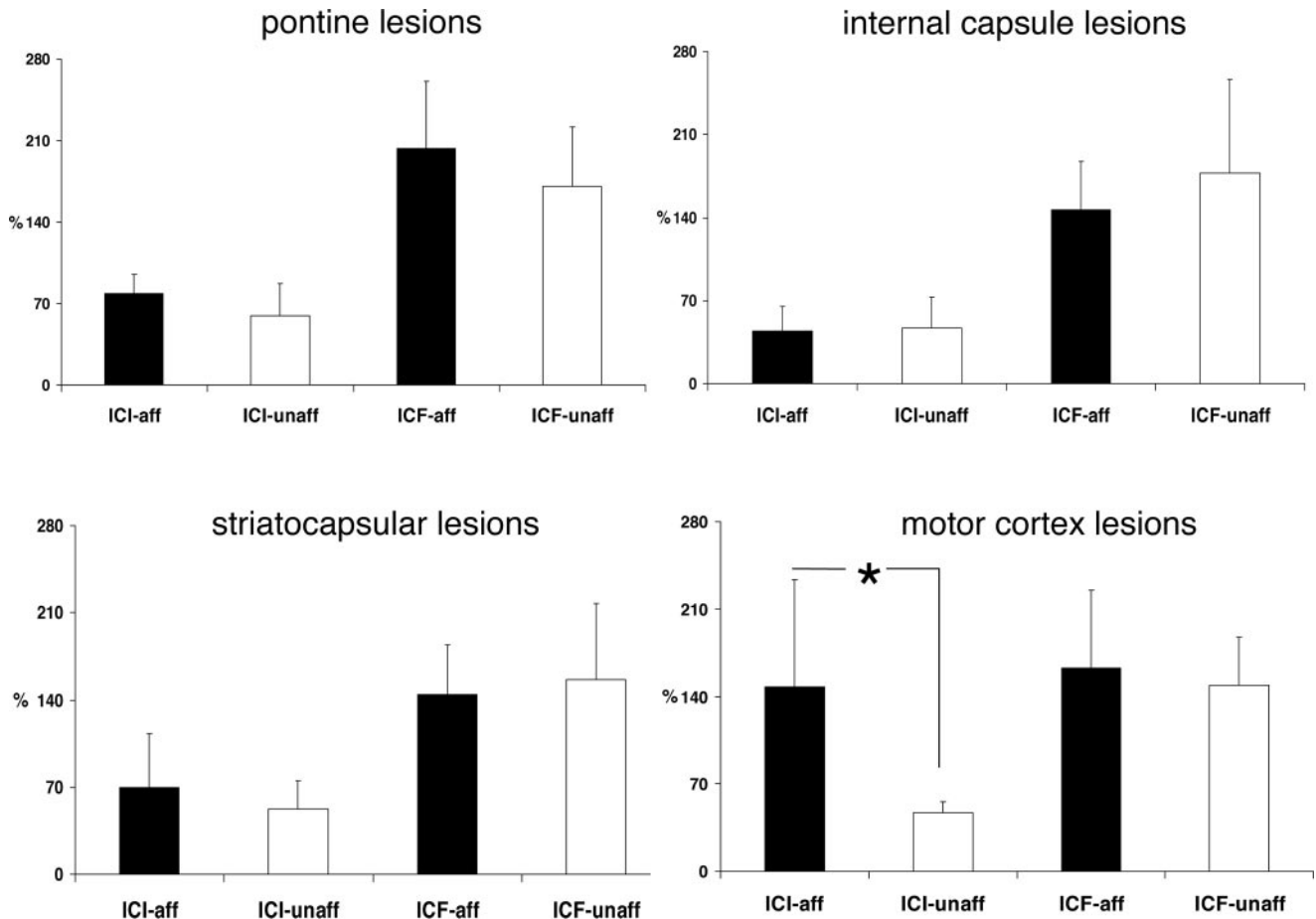
Figure 3. ICI and ICF in the 4 stroke groups; black bars represent the affected side, open bars demonstrate the unaffected side. Vertical axis: MEP amplitudes expressed as percentage of the mean single pulse MEP amplitude. *$P<0.05$.

Correlations of Motor Performance With TMS Results

In the PL group, 9-HPT results were significantly correlated with the MT ($r=0.669$), maximum MEP amplitudes ($r=-0.842$), and 140% intensity SRC ($r=-0.683$). In the IC group, 9-HPT performance was correlated with SP duration ($r=0.643$), 110% intensity SRC ($r=-0.555$), and the MT ($r=0.553$). In the M1 group and the SCL group, there was no correlation between 9-HPT or grip strength and any electrophysiological parameter. 9-HPT performance and grip strength were significantly correlated with each other (PL group: $r=-0.927$; IC group: $r=-0.621$; M1 group: $r=-0.81$; SCL group: $r=-0.65$).

Discussion

This study was performed with carefully selected acute stroke patients. They represented a clinically homogeneous group but differed according to their lesion location and the inhibitory and excitatory properties of their brains. One main conclusion from this study, therefore, is that the site of the lesion determines the pattern of brain excitability changes.

An ischemic M1 lesion was associated with a loss of ICI. We suggest that this disinhibition, rather, is a direct consequence of the lesion than some compensatory mechanism, because a similar phenomenon was not observed in internal capsule lesions despite the comparability in clinical appear-

ance. M1 lesions also showed a different pattern in the duration of the SP, which tended to be shorter on the affected side. In contrast, subcortical lesions (PL, IC, and SCL) were associated with SP prolongations on the affected side. The shortened SP in M1 lesions has been reported earlier[16] and reflects a reduced activity of an inhibitory intracortical network, corresponding to the disinhibition observed in the paired-pulse experiments. Both ICI and SP duration can be modified by GABAergic drugs,[17] and it has been described that GABAergic neurons are particularly susceptible to ischemic or hypoxic damage.[18] Therefore, our results may indicate an ischemia-induced impairment of GABAergic neurotransmission. MTs as an indicator of corticospinal excitability were nonsignificantly elevated in the affected hemisphere. Most probably, the increased MTs indicate a lesion of motor neurons or axons with the lowest thresholds. The stimulus response curve, which explores the recruitment behavior of neurons with higher MTs, showed reduced MEP amplitudes on the affected side when stimulating with the highest stimulus intensity. There are at least 2 possible explanations for this side-to-side difference: (1) neurons with high MTs could have been particularly susceptible to ischemia; however, this idea seems to contradict the observation of increased MTs; and (2) neurons with the lowest MTs were damaged during ischemia, thus inducing an MT rise. Because the stimulus intensity for the SRC was adjusted to the

individual MT, even stimulus intensities close to the MT could then have been sufficient to stimulate high-threshold neurons. Thus, a ceiling effect (no additional increase of MEP size despite increasing stimulus intensity[19]) could have occurred with relatively lower stimulus intensity. Presumably, ischemia also damaged neurons with higher MTs. This scenario automatically implies that differences between affected and unaffected hemispheres become more prominent with increasing stimulus intensities, which was true for the M1, PL, and IC groups.

In the PL and IC groups, many similarities were found. First, both stroke types present with a rather small but strategically unfavorable lesion being located in the course of the corticospinal motor tract. In both, the MT is elevated in the affected hemisphere, and the SRC shows a smaller increase of MEP size with increasing stimulus intensities, although this difference between the affected and unaffected side was more prominent in the PL group. Presumably, the small slope of the SRC is attributable to 2 factors: (1) the lesion has reduced the number of corticospinal neurons or axons accessible by TMS; and (2) we assume that the MEP amplitude increase is less steep, because a majority of the high-threshold neurons became activated with stimulus intensities close to the MT, thus causing a ceiling effect. The SP obtained from the affected side was prolonged in the PL and IC groups. This finding is consistent with earlier reports[16,20,21] and indicates that subcortical lesions increase the activity of inhibitory neuronal circuits. It is assumed that this enhanced intracortical inhibitory activity is because of a deafferentation of the primary motor cortex by different lesions outside M1.[21] Interestingly, intracortical excitability tested with the paired-pulse paradigm was unchanged in the affected hemisphere. This suggests that pure subcortical lesions affecting the corticospinal tract do not influence ICI or ICF to a relevant degree, in contrast to a cortical lesion. Other reports have shown that changes of ICI and ICF may occur if central sensory afferents are impaired[22,23] or if the superior cerebellum is lesioned.[24] Thus, in general, intracortical excitability can be modulated by lesions anatomically distant from the primary motor cortex. However, the exact location of the infarct is crucial for modification of ICI or ICF.

The SCL group represents a different type of subcortical infarct. Usually, these lesions indicate a large-vessel disease and are either produced by a stenosis of the middle cerebral artery trunk or by an embolic occlusion of this vessel. The area affected by the ischemia is larger than in lacunar lesions. Motor impairment was similar to the other groups, but the side-to-side comparison of the TMS data only indicated one relevant difference: the SP duration was prolonged in the affected side. All of the other parameters showed no significant difference. Thus, motor impairment in our SCL patients is probably not because of a relevant affection of the corticospinal tract. Possibly, the enhanced activity of inhibitory cortical neurons contributes to the impaired motor functions.[21] Neuronal circuits within the basal ganglia facilitate the motor cortex either through antidromic excitation of cortical-basal ganglia fibers or through orthodromic activation of a basal ganglia-thalamocortical pathway.[25,26] Therefore, an ischemia-induced disturbance of the basal ganglia

may result in changes of motor excitability and motor performance.

Correlation of Motor Excitability and Motor Performance

In the IC group, a correlation between SP duration and 9-HPT results was found, indicating that the longer the SP was, the worse the subject's dexterity was. Others have also described an association between SP and an impairment of movement initiation.[21] In subcortical lesions (PL and IC group), the MT was correlated with dexterity measured by the 9-HPT. This finding suggests that the MT as a basic parameter of corticospinal excitability is closely associated with motor function. It corresponds with earlier reports in which the MT was found to be a good predictor of the recovery of function after stroke[27,28] or was correlated with muscle strength in the paretic limb.[29,30]

In summary, our results demonstrate that lesions affecting the primary motor cortex induce a different pattern of excitability changes than subcortical lesions do. Together with results published elsewhere,[22–24] our present data suggest that pure motor strokes are associated with excitability changes that differ substantially from lesions with impairment of central sensory afferents. Therefore, it is recommendable that, in future studies, stroke patients should be selected carefully in relation to their lesion location in order to make groups as homogeneous as possible.

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