Disinhibition of the Premotor Cortex Contributes to a Maladaptive Change in the Affected Hand After Stroke

Naoyuki Takeuchi, MD, PhD; Takeo Tada, MD, PhD; Takayo Chuma, MD; Yuichiro Matsuo, MD; Katsunori Ikoma, MD, PhD

Background and Purpose—The mechanism of reorganization after stroke remains uncertain. Several studies that have measured reaction time (RT) delay by transcranial magnetic stimulation (TMS) have revealed some substrates responsible for the reorganization of motor recovery. In this study, we evaluated the RT delay and inhibitory functions by examining the silent period (SP) in the primary motor cortex (M1) and premotor cortex (PMC) of the affected hemisphere. Using these data, we investigated whether a change in the inhibitory system might influence motor recovery.

Methods—This study was performed in 20 patients with chronic subcortical stroke. To evaluate the RT delay, TMS was applied to the affected hemisphere 100 ms after showing the cue that indicated paretic finger movement. The SP was induced by TMS over the affected hemisphere during voluntary contraction of the paretic hand.

Results—The RT delays of the PMC were more prominent in patients with greater disability. The ratio of SP duration to RT delay in the PMC decreased with the decline in motor function. Moreover, upper arm function was better than hand function in patients with a decreased SP in the PMC.

Conclusions—The inhibitory function of the PMC was disturbed in patients with poor motor function. Stroke patients with poor motor ability appeared to depend not only on the motor pathway from M1 but also on other parallel motor circuits to move the paretic side. However, this brain reorganization might result in the sacrifice of function of the affected hand. (Stroke. 2007;38:1551-1556.)

Key Words: disinhibition ■ stroke ■ transcranial magnetic stimulation

Functional imaging techniques have revealed a negative correlation between activation of secondary motor networks and motor function after stroke.1,2 The role of the ipsilesional primary motor cortex (M1) is undoubtedly important for recovery of the affected hand;3 however, it remains uncertain whether the activation of a motor-related area outside the ipsilesional M1 contributes to a maladaptive change or true recovery.4–6

In recent studies, reaction time (RT) delays induced by transcranial magnetic stimulation (TMS) have been considered for revealing the sites that contribute to motor recovery after stroke.3,7,8 TMS temporarilly delays but does not distort the execution of a motor command stored in strategically placed neurons within the neural substrate that is responsible for the motor response.9 Therefore, a site where an RT delay was induced by TMS when a subject moved the paretic hand could be interpreted as the site contributing to motor recovery.

In this study, we investigated the correlation between RT delay and silent period (SP) duration in the M1 and premotor cortex (PMC) of the affected hemisphere. It has been reported that SP duration is considered to reflect an inhibitory function of cortical origin10,11 and that RT delay is correlated with SP duration in healthy subjects.10,12,13 However, we hypothesized that the SP duration in stroke patients might decrease compared with the RT delay at a site that contributed to the reorganization of the brain, particularly if this site was outside the M1. This hypothesis was formulated because several studies reported that a reduction in inhibitory function contributed to cortical plasticity.4,14 In addition, we examined the correlation between the SP of the PMC and motor recovery to study whether a change in the inhibitory system of the PMC influences reorganization in the hand and upper arm regions of the cortex.
Electromyographic (EMG) activity was recorded with Ag-AgCl electrodes positioned in a belly tendon montage on the skin overlying the first dorsal interosseous (FDI) muscle. The signal was amplified, filtered (50 to 2000 Hz), and digitized at a sampling rate of 5000 Hz for off-line analysis (Neuropack; Nihon Koden, Tokyo, Japan). A figure-of-8 magnetic coil was used for TMS. The coil was placed tangentially over the M1 at an optimal site for the FDI muscle. The optimal site was defined as the location where stimulation of a slightly suprathreshold intensity elicited the largest motor-evoked potentials in the FDI muscle. The resting motor threshold (rMT) was measured at the optimal site and was defined as the lowest stimulator output that could elicit motor-evoked potentials with peak-to-peak amplitudes >50 μV in at least half of 10 trials.

The RT experimental paradigm was displayed on a screen with the use of Labview (National Instruments, Austin, Tex). Each patient was comfortably seated in an armchair, 60 cm in front of a computer screen positioned at eye level. After a training session (3 blocks of 25 trials each), each participant was instructed to perform index-finger flexion movements as quickly as possible in response to a randomly (5- to 9-second) displayed “go” signal. TMS was delivered 100 ms after the “go” signal; its intensity was 80% of the maximum stimulator output. The order of stimulating the sites under examination (the M1, the PMC, and a sham stimulation) was randomized after the “go” signal and the onset of the EMG burst (defined as the time when the EMG amplitude exceeded the mean value +3 SDs of the EMG amplitude in the 100 ms preceding the “go” signal). The RT at each site was determined for 25 averaged responses. In addition, the RT delay at each site was defined as the difference between the RT at each site and the RT in the case of sham stimulation.

We examined the SP duration of FDI muscle activity evoked by TMS at an intensity of 80% of the maximum stimulator output, during 20% of the maximal voluntary contraction of FDI muscle, and with visual feedback of muscle activity. Moreover, we used a stimulus at 130% of the rMT to exclude the possibility that a stimulus at a fixed level of stimulator output could not completely activate the inhibitory neurons in patients with a high rMT. The SP duration was measured in a single-trial EMG as the duration between the TMS stimulus and the first recurrence of a sustained, voluntary EMG. The mean of 5 trials was used for further analysis. We excluded 6 patients who did not display the SP phenomenon from the SP study section, ie, an SP was not induced during tonic contraction, even with 100% stimulator output. For comparison of the SP duration relative to the RT delay at each site, the ratio of SP to RT was defined as SP duration/RT delay. Because RT delay was correlated with SP duration, the disturbance of the inhibitory system increased with a decrease in the ratio of SP to RT. The RT delay induced by TMS was analyzed by repeated-measures ANOVA followed by a post hoc analysis with Scheffe’s F test. Possible correlations among the various parameters were determined with Pearson’s correlation coefficient test.

### Results

The rMT of the patients with stroke was 65.1±4.3%. It tended to be higher in patients with poor recovery than in those with good motor performance. However, no significant correlation was observed between the rMT and FMS score ($r = -0.430, P = 0.059$).

<table>
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<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Duration After Stroke, mo</th>
<th>Paretic Side</th>
<th>FMS for Upper Limb, %</th>
<th>FMS for Arm, %</th>
<th>FMS for Hand, %</th>
<th>Lesion Site</th>
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<td>R</td>
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<td>100</td>
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<td>Putamen and corona radiata</td>
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Mean±SD 52.5±14.4 27.4±18.2 67.7±23.8 71.9±24.0 60.2±25.3
A repeated-measures ANOVA revealed a significant difference among RT delays at the stimulation sites \( F(2, 38) = 44.10, P < 0.001 \). Post hoc testing revealed that an increase in RT was apparent in the M1 and PMC when compared with the RT induced after sham stimulation (M1 \( P < 0.001 \), PMC \( P < 0.001 \)). The RT delay was significantly associated with the SP in the M1 (\( r = 0.934, P < 0.001 \)), but the RT delay was not significantly associated with the SP in the PMC (\( r = 0.272, P = 0.347 \)).

Table 2 shows correlations between motor function and the electrophysiologic data. The RT delay of the PMC was negatively correlated with the FMS score (\( r = -0.787, P < 0.001 \); Figure 3a). However, the RT delay of the M1 was not correlated with the FMS score. The ratio of SP to RT in the M1 was not significantly associated with the FMS score. However, the ratio of SP to RT in the PMC was significantly associated with the FMS score (at fixed power, \( r = 0.563, P = 0.036 \), Figure 3b; at 130% rMT, \( r = 0.595, P = 0.025 \)). This result indicated that compared with the RT delay, the SP of the PMC decreased with the decline in motor function. Moreover, the decreased ratio of SP to RT in the PMC was

Figure 1. Examples of the raw data. a, A patient with good motor function and (b) a patient with poor motor function. TMS over the M1 induced an RT delay in individual patients with good and poor motor function. However, the RT delay of the PMC was more prominent in patients with poor motor function than in those with good motor function. Compared with the RT delay, the SP duration of the PMC was shorter in patients with poor motor function than in patients with good motor function.

![Figure 1](image1)

Figure 2. The RT change induced by TMS over each site. *\( P < 0.05 \), **\( P < 0.01 \). Error bar is the SD.

![Figure 2](image2)
correlated negatively with the ratio of the upper arm subset to the hand subset of the FMS (at fixed power, \( r = -0.704, P = 0.005 \), Figure 3c; at 130% rMT, \( r = -0.689, P = 0.006 \)).

### Discussion

The RT delays after TMS over the ipsilesional PMC were more prominent in patients with greater disability. In contrast, patients with good motor function demonstrated normal RT delay patterns of the paretic hand similar to those in healthy controls; RT delays induced by TMS were found in the contralateral M1 but not in the PMC.\(^{13,19}\) These results indicated that the patients with good motor function had normal activation patterns during their hand movements because control from the PMC was either less important or suppressed. However, in patients with poor motor function, the motor control of the affected hand was dependent on the motor pathway from not only the M1 but also the PMC. This finding is consistent with that of a neuroimaging study that reported a negative correlation between motor function and multiple motor-related activations.\(^{1,2}\) From another viewpoint, simple movements performed after stroke may require extensive motor cortical activity, similar to that associated with the more complex movements of “choice reaction time” of healthy controls. Other studies have noted that TMS over the contralateral PMC can induce RT delays during choice reactions of healthy controls.\(^{19,20}\)

In healthy controls, a correlation between SP duration and RT delay has been noted.\(^{10,13}\) This study also demonstrated a positive correlation between SP duration and RT delay of the affected M1 areas in stroke patients. However, in the PMC, SP duration was not correlated with RT delay, and we found that, compared with the RT delays, the SP durations of the PMC decreased with the decline in motor function. It has been postulated that the SP may reflect \( \gamma \)-aminobutyric acidergic inhibition of the cerebral cortex.\(^{10,21}\) Several studies have reported that the loss of perilesional \( \gamma \)-aminobutyric acidergic inhibition contributes to the reorganization of the brain after stroke. This occurs by the unmasking of preexcitatory, functionally latent neural networks around the lesion and by an increased excitatory neurotransmitter release via removal of the inhibition of excitatory inputs.\(^{4,14}\) The decreased SP duration in patients with poor motor function might reflect a disturbance in inhibitory function and the unmasking of latent excitatory connections in the PMC. Furthermore, this decreased SP duration of the PMC showed a negative correlation with relatively good function of the upper arm when compared with that of the hand. The projections from the PMC to the spinal cord are known to be less numerous and less excitatory than those from the M1.\(^{22,23}\) Moreover, the projections from the PMC are more concerned with the control of muscle movements of the upper arm.\(^{24,25}\) Regarding reorganization, it has been reported that hand and upper arm regions compete for areas within the cortex.\(^{26}\) Considering these findings, the excitability that is unevenly distributed in the upper arm due to weak inhibitory function of the PMC might cause poor reorganization of the cortex that controls the hand. This hypothesis is consistent with the fact that the function of the upper arm was better than that of the hand in chronic stroke patients.\(^{26,27}\)

We observed that the SP duration of the PMC by stimulation at a fixed level of stimulator output was relatively decreased compared with the RT delay in patients with poor motor function. However, there is a possibility that fixed-power stimulation did not completely activate inhibitory neurons in patients with poor motor function after stroke. In these patients, the rMT was often high; therefore, to overcome this problem, we used 130% of the rMT as the stimulus while studying SP duration. The SP duration of the PMC by 130% of the rMT stimulation, compared with the RT delays, decreased with the decline in motor function, as well as fixed-power stimulation. This result suggested that the decrease in SP duration of the PMC in these patients (poor motor function after stroke) was a peculiar epiphenomenon and did not occur due to insufficient stimulation power. The RT delay induced by fixed-power stimulation of the PMC was more prominent in patients with greater disability, who often had a high rMT. The power of the TMS had a positive correlation with RT delay.\(^{10,13}\) It was considered that stimulation with 130% of the rMT might be more powerful and induce more prolonged RT delays in patients with poor motor function than those induced by fixed-power stimulation. Similarly, it was thought that the ratio of SP to RT in the PMC would have a more significant correlation with motor function, because the ratio of SP that was compared with the more prolonged RT delay after stimulation with 130% of the rMT might decrease more than fixed-power stimulation in patients with poor motor function. Because there was no possibility that an RT study with a stimulation of 130% of the rMT would have an outcome different from that obtained by the study with fixed-power stimulation, we did not conduct an RT study at 130% of the rMT.

Several studies have reported that the ipsilesional dorsal premotor cortex (PMd), particularly that in the PMC, plays an important role in motor recovery after stroke.\(^{15,17}\) We did not stimulate the PMC by specifying the PMd in this study. Therefore, to enhance understanding of the role of the PMC

### Table 2: Correlations Between Motor Function and Electrophysiologic Data (Correlation Coefficients and \( P \) Values)

<table>
<thead>
<tr>
<th>Upper limb subset of FMS</th>
<th>RT Delay (M1)</th>
<th>RT Delay (PMC)</th>
<th>SP (M1)</th>
<th>SP (PMC)</th>
<th>At Fixed Power</th>
<th>At 130% of rMT</th>
<th>At Fixed Power</th>
<th>At 130% of rMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of upper arm subset to hand subset of FMS</td>
<td>-0.328 (0.158)</td>
<td>0.211 (0.371)</td>
<td>-0.069 (0.814)</td>
<td>-0.431 (0.123)</td>
<td>-0.436 (0.119)</td>
<td>-0.489 (0.076)</td>
<td>-0.704 (0.005)†</td>
<td>-0.689 (0.006)†</td>
</tr>
</tbody>
</table>

\( ^{*}P<0.05, \dagger P<0.01. \)
in poststroke motor recovery, further studies are required to accurately stimulate the PMd by a stereotactic system integrated with magnetic resonance imaging data.

In conclusion, it appears that patients with poor motor function may use motor-related regions such as the PMC to move the paretic side. Disinhibition of the ipsilesional PMC might partly contribute to the reorganization of the brain in stroke patients with poor motor function. However, large-scale reorganization outside the ipsilesional M1 is a lengthy process that never results in complete recovery.

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Disclosures
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