Reversal of Cortical Reorganization in Human Primary Motor Cortex Following Thumb Reconstruction

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Ni Z, Anastakis DJ, Gunraj C, Chen R. Reversal of cortical reorganization in human primary motor cortex following thumb reconstruction. J Neurophysiol 103: 65–73, 2010. First published November 11, 2009; doi:10.1152/jn.00732.2009. Deafferentation such as the amputation of a body part causes cortical reorganization in the primary motor cortex (M1). We investigated whether this reorganization is reversible after reconstruction of the lost body part. We tested two patients who had long-standing thumb amputations followed by thumb reconstruction with toe-to-thumb transfer 9 to 10 mo later and one patient who underwent thumb replantation immediately following traumatic amputation. Using transcranial magnetic stimulation, we measured the motor evoked potential (MEP) threshold, latency, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) at different time points in the course of recovery in abductor pollicis brevis muscle. For the two patients who underwent late toe-to-thumb transfer, the rest motor threshold was lower on the injured side than that on the intact side before surgery and it increased with time after reconstruction, whereas the active motor threshold remained unchanged. The rest and active MEP latencies were similar on the injured side before and ≤15 wk after surgery and followed by restoration of expected latency differences. SICI was reduced before surgery and progressively normalized with the time after surgery. ICF did not change with time. These physiological measures correlated with the recovery of motor and sensory functions. All the measurements on the intact side of the toe-to-thumb transfer patients and in the patient with thumb replantation immediately following traumatic amputation remained stable over time. We conclude that chronic reorganization occurring in the M1 after amputation can be reversed by reconstruction of the lost body part.

INTRODUCTION

Brain plasticity, defined as any morphological or functional changes in cortical properties (Sanes and Donoghue 2000), can be either beneficial (Cohen et al. 1997) or maladaptive (Flor et al. 1995). Transcranial magnetic stimulation (TMS) can be used to examine the excitability of the human primary motor cortex (M1) and provide insights into the mechanisms of plasticity occurring in M1 (Tyc and Boyadjian 2006). Reorganization caused by plasticity occurs in the M1 in response to a variety of experiences, from learning to play a musical instrument (Nordstrom and Butler 2002), losing a limb (Chen et al. 1998a), to restoration of motor functions through muscle transfer (Chen et al. 2003).

Motor evoked potential (MEP) amplitude elicited by TMS and motor threshold are measures of corticospinal excitability (Rothwell 1997). Muscle activation shortens the MEP latency by several milliseconds compared with that of the rest condition (Weber and Eisen 2002). Intracortical neuronal circuits in the M1 can be examined by a conditioning-test TMS paradigm. When a subthreshold conditioning stimulus (CS) is followed by a suprathreshold test stimulus (TS) at interstimulus intervals (ISIs) of 1–5 ms, CS inhibits the MEP generated by TS, a phenomenon referred to as short-interval intracortical inhibition (SICI). On the other hand, at ISIs of 6–15 ms, facilitation is elicited, a phenomenon known as intracortical facilitation (ICF) (Kujirai et al. 1993; Ziemann et al. 1996c). Many studies have suggested that SICI is mediated by a γ-aminobutyric acid type A (GABA_A) receptor (Ziemann et al. 1996a,c). The mechanisms underlying ICF are not fully understood. Excitatory glutamatergic interneurons and N-methyl-D-aspartate receptors appear to influence ICF (Ziemann et al. 1998a). However, unlike SICI and other intracortical circuits, changes in descending corticospinal volleys are not associated with this facilitation (Di Lazzaro et al. 2006). Previous studies found that cortical reorganization occurs in the M1 when the limbs are deafferented. Short-term plasticity can be demonstrated with about 30 min of ischemic nerve block together with low-frequency repetitive TMS of the deafferented M1. This plastic change is manifested by increased MEP size, decreased SICI, and increased ICF (Ziemann et al. 1998b). This effect can last ≥60 min after removal of ischemic nerve block, suggesting that acute deafferentation causes plastic change in M1 and this plastic change is reversed by reafferentation after the ischemic nerve block is removed. Chronic deafferentation leads to more pronounced and long-term reorganization in the M1. In patients with lower-limb amputation, both motor threshold and SICI decreased for the muscle immediately proximal to the amputation, suggesting that increased excitability of the corticospinal neurons and the reduction of GABA_A activity at the cortical level may mediate this type of reorganization (Chen et al. 1998a). These studies raised important questions with respect to whether the chronic reorganization in the M1 is reversible and what the time courses of these changes are. To address these questions, we had the rare opportunity to test two patients who underwent thumb reconstruction with toe-to-thumb transfer 9 to 10 mo after amputation. We also tested one patient who underwent thumb replantation immediately after traumatic amputation as a control. We hypothesized that chronic reorganization occurs in the M1 after amputation, that this reorganization is reversible after reafferentation of the lost body part, and that the reversal of reorganization brought about by plasticity would correlate with recovery of motor and sensory functions.
METHODS

Patients

Three right-handed men participated in the study. Handedness was confirmed using the Oldfield Handedness Inventory (Oldfield 1971). Patient 1 was a 23-year-old carpenter who sustained a traumatic left-thumb amputation. He underwent microvascular transfer of the left great toe to his left thumb 10 mo after the injury. Patient 2 was a 19-year-old laborer who injured his left hand while making a homemade bomb. The injury resulted in amputation of the thumb and index finger at the metacarpal neck. He underwent microvascular transfer of his left great toe to his left thumb 9 mo after the injury. Patient 3 was a 30-year-old grocery store worker who sustained an amputation of the left thumb at the midproximal phalanx level while working with a table saw. Replantation of the thumb was performed within 3 h of the injury by shortening the thumb and fusing the interphalangeal joint. All patients provided written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University Health Network (Toronto) Research Ethics Board.

Measurements of plasticity over the course of recovery

To identify changes in cortical plasticity over time, we measured several parameters during the course of recovery. These measurements included examination of motor and sensory functions, rest and active motor thresholds (RMT and AMT) for TMS, MEP latencies in the rest and active states, SICI, and ICF. Patient 1 was studied before and at 14, 35, and 105 wk after surgery. Patient 2 was studied before and at 9, 15, 34, and 52 wk after surgery. Patient 3 was studied 8, 13, 40, and 60 wk after surgery.

Testing of motor and sensory functions

Thumb motor function was assessed using key pinch and interphalangeal joint active range of movement (IPJ ROM). Thumb sensory function was assessed using Semmes–Weinstein monofilament (SWM) and two-point discrimination (2PD) performed on the thumb (innervated by median nerve) and the little finger (innervated by the ulnar nerve). Key pinch was examined on both sides and IPJ ROM, SWM, and 2PD were examined on the injured side only. The motor and sensory functions were assessed only after surgery since there was no thumb on the injured side before surgery. For Patients 2 and 3, the key pinch test and 2 PD test were not completed at their first visit after surgery (9 wk for Patient 2; 8 wk for Patient 3). Key pinch test involved maximum force to complete the task and was not considered safe at that stage of the recovery.

EMG recording

Surface electromyograms (EMG) were recorded from the left (injured side) and right (intact side) abductor pollicis brevis (APB) muscles with 9-mm-diameter Ag–AgCl surface electrodes. APB muscle was selected because it is just proximal to the thumb and was not injured. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the thumb. The signal was amplified (×1,000), band-pass filtered (2 Hz to 2.5 kHz; Model 2024F, Intronix Technologies, Bolton, Ontario, Canada), digitized at 5 kHz by an A/D interface (Micro1401; Cambridge Electronics Design, Cambridge, UK), and stored in a computer for off-line analysis. The EMG signal passed through a leaky integrator and the EMG level was displayed to the subject on an oscilloscope. For recording of AMT and active SICI/ICF, the subjects contracted the APB muscle to produce 20% of maximum EMG with the aid of visual and auditory feedback.

Transcranial magnetic stimulation

Two Magstim 200 stimulators, one Bistim Module (Magstim, Whitland, Dyfed, UK), and a figure-of-eight shaped coil (outside diameter of each loop was 9.5 cm) were used to apply TMS. The two stimulators were connected to the Bistim Module, which was connected to the TMS coil. The handle of the coil pointed backward at 30–45° from the midsagittal line. The induced current in the brain was directed anterior-medially, approximately perpendicular to the central sulcus. With this current direction, pyramidal neurons are activated transynaptically (Di Lazzaro et al. 2001; Kaneko et al. 1996). The optimal position for activation of the contralateral APB muscle was marked with a pen as the motor hot spot. The TMS coil was placed over the hot spot to the target muscle. The injured and intact sides were studied separately. The hot spot on each side was assessed at each time point before and after surgery.

Motor threshold

RMT was defined as the minimum stimulator output that induced MEPs of >50 μV in ≥5 of 10 consecutive trials when the target muscle was completely relaxed. AMT was defined as the minimum stimulator output that induced MEPs of >200 μV in ≥5 of 10 consecutive trials during voluntary muscle contractions of 20% maximum. We also measured the intensity for 1-mV MEP, which was defined as the minimum intensity to generate MEPs of >1 mV in ≥5 of 10 consecutive trials when the target muscle was completely relaxed.

Short-interval intracortical inhibition and facilitation

We measured SICI and ICF using a CS–TS paired-pulse paradigm. An ISI of 2 ms was selected to investigate SICI and 10 ms was selected to investigate ICF. Since voluntary contraction changes SICI and ICF (Ridding et al. 1995) and the finding for SICI with voluntary contraction was different from that at rest for some settings of cortical plasticity such as free functioning muscle transfer (Chen et al. 2003), SICI and ICF were measured at rest and in the active state (20% of maximum EMG). TS was set to generate 1-mV MEPs with the targeted muscle relaxed. The same TS was used for both the rest and the active conditions. CS intensity was set at 0.8 RMT for the rest condition and at 0.95 AMT for the active condition. Ten trials for each ISI (2 and 10 ms) and TS alone (total of 30 trials) were delivered in random order. Data for rest and active conditions were collected in separate runs.

Data analysis

MEP latencies were measured from TMS delivery to the MEP onset. To compare the resting and active MEP latencies, we calculated the ratio of MEP latency at rest to that in the active condition at each time point. MEP amplitudes were measured peak to peak. The MEP amplitudes evoked by paired-pulses (CS–TS) were expressed as a percentage of the mean MEP amplitude of TS alone. Values <100% indicate inhibition and values >100% indicate facilitation. Unless otherwise stated, values are reported as means ± SD.

Statistical analysis

Separate analyses were performed in each patient. The relationship between RMT, AMT, intensity for 1-mV MEP, and time after surgery were examined by Pearson’s correlation coefficient. The time point before surgery (Pre) in Patients 1 and 2 was set at 0. A two-way repeated-measures ANOVA with muscle side (injured vs. intact) and time as the within-subject factors was used to examine the rest to active MEP latency ratios. A two-way repeated-measures ANOVA with side (injured vs. intact) and time as the within-subject factors was...
conducted to examine the difference for SICI and ICF. Post hoc testing using an unpaired t-test with Bonferroni correction for multiple comparisons was performed to examine at which time points the measurements were different from each other. In addition, we compared the SICI in Patients 1 and 2 with a control group reported in a previous study (Chen et al. 1998b) by calculating Z-scores. We further examined the relationships between physiological measures and measures of motor and sensory functions using Pearson’s correlation coefficient. RMT and SICI were the selected physiological measures because they showed significant change over time in Patients 1 and 2 (see RESULTS). They were normalized as the ratios between injured and intact sides because the absolute values vary depending on the different experimental days. Motor and sensory functions used were key pinch and SWM performed on the injured thumb after surgery. StatView (5.0.1) software was used for statistical analysis. The significance level was set at P < 0.05.

RESULTS

Motor and sensory functions

Table 1 shows the clinical measures of motor and sensory functions in the three patients after surgery. All the functions showed substantial recovery within 6 mo after the toe-to-thumb transfer or thumb replantation.

Rest and active motor threshold

The data for RMT and AMT in the three patients are shown in Table 2. Figure 1A shows the results for Pearson’s correlation test that RMT on the injured side significantly increased with the time after surgery for Patients 1 and 2 [Patient 1: R² = 0.96, F(1,2) = 45.84, P = 0.021; Patient 2: R² = 0.78, F(1,3) = 10.80, P = 0.046]. For Patient 3, there was no significant change of RMT with time. The RMT on the intact side did not change with time for all three patients. Figure 1B shows the time courses of AMT. There was no significant effect of time on AMT for the injured or intact sides. The stimulus intensities required to generate 1-mV MEP are shown in Fig. 1C. On the injured side, the intensity significantly increased with the time for Patient 1 [R² = 0.98, F(1,2) = 125.97, P = 0.008] and Patient 2 [R² = 0.83, F(1,3) = 14.41, P = 0.032], but not for Patient 3. This intensity did not change with time on the intact side.

MEP latency

Table 2 shows that MEP latencies on the injured side were similar at rest and at active conditions before and shortly after surgery in Patients 1 and 2. With the time of recovery MEP latency at rest became longer than that at the active condition. Finally, the difference in MEP latencies between two states became about 2 ms and this difference was comparable with that on the intact sides in these patients and with that on both sides in Patient 3. Figure 2 shows the rest to active MEP latency ratios in the three patients. For Patients 1 and 2, ANOVA showed significant main effects of side (injured vs. intact) [Patient 1, F(1,27) = 43.28, P < 0.001; Patient 2, F(1,36) = 22.31, P = 0.001] and time [Patient 1, F(3,27) = 5.52, P = 0.004; Patient 2, F(3,36) = 3.37, P = 0.019]. The side and time interaction was also significant [Patient 1, F(3,27) = 3.12, P = 0.042; Patient 2, F(4,36) = 6.24, P < 0.001], indicating that the effects of time were different on the injured and intact sides. Figure 2 shows that on the injured side the rest and active MEP latencies were similar before and shortly after surgery and the expected longer latencies for rest MEP were restored over time. On the intact side, the rest to active MEP latency ratios were stable over time. For Patient 3, no significant main effect or the interaction between main effects was found. Further post hoc tests confirmed that the smaller ratios on the injured side compared with those on the intact side before and at 14 wk after surgery (P < 0.01 for both comparisons) in Patient 1; and before and 9 and 15 wk after surgery (P < 0.01 for before and 9 wk after surgery; P < 0.05 for 15 wk after surgery) in Patient 2.

Short-interval intracortical inhibition

SICIs at various time points on the recovery course for three patients are listed in Table 2. Figure 3A shows that on the injured side of the two patients with late reafferentation by toe-to-thumb transfer, SICI at rest was absent before surgery and increased over time but remained unchanged on the intact side and on both sides in the patient with immediate thumb replantation. ANOVA showed significant main effects of side (injured vs. intact) [F(1,27) = 10.00, P = 0.012] and time [F(3,27) = 4.67, P = 0.009] on SICI for Patient 1. The interaction between side and time was also significant [F(3,27) = 3.65, P = 0.025]. Figure 3A shows that this is because SICI on the injured side increased with time, but there was little change on the intact side. Post hoc tests found the reduced SICI on the injured side compared with the intact side before and at 14 wk after the surgery (P < 0.05 for both comparisons). We further compared the SICI at each time point with a control group in a previous study by generating Z-scores. With the same exper-

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<thead>
<tr>
<th>Time after surgery, wk:</th>
<th>14</th>
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<th>15</th>
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<th>52</th>
<th>8</th>
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<th>40</th>
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<tr>
<td>Key pinch injured side, kg</td>
<td>2.0</td>
<td>10.5</td>
<td>12.5</td>
<td>—</td>
<td>2.0</td>
<td>3.5</td>
<td>4.0</td>
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<td>4.0</td>
<td>6.5</td>
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<tr>
<td>Key pinch intact side, kg</td>
<td>7.0</td>
<td>12.0</td>
<td>10.5</td>
<td>—</td>
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<td>IPJ ROM, deg</td>
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<td>SWM thumb</td>
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<td>SWM little finger</td>
<td>4.31</td>
<td>4.08</td>
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<td>4.08</td>
<td>3.84</td>
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<td>2PD thumb, mm</td>
<td>10.0</td>
<td>10.0</td>
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<td>2PD little finger, mm</td>
<td>10.0</td>
<td>10.0</td>
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IPJ ROM, interphalangeal joint active range of movement; SWM, Semmes–Weinstein monofilament; 2PD, two-point discrimination; —, not tested. Note: IPJ ROM values from Patient 3 are “0” at any time because the replantation of the thumb was performed by shortening the thumb and fusing the interphalangeal joint.
The SICI in 11 normal subjects was 42.4 ± 22.0% in that study (Chen et al. 1998b). The results confirmed that SICI on the injured side was abnormal before (Z = 11.49, P < 0.001) and at 14 wk after the surgery (Z = 4.84, P < 0.001). At these two assessments, the inhibition turned into facilitation. For Patient 2, the effect of injured versus intact side [F(1,36) = 16.48, P < 0.003] and the interaction between side and time [F(4,36) = 2.90, P = 0.035] were significant, but the main effect of time was not significant. Post hoc tests found lower SICI on the injured side compared with the intact side before and at 9 and 15 wk after the surgery (P < 0.05 for all comparisons). Compared with the control group (Chen et al. 1998b), SICI in 11 normal subjects was 42.4 ± 22.0%.

TABLE 2. Physiological measures in left (injured side) and right (intact side) APB muscles in Patients 1, 2, and 3

<table>
<thead>
<tr>
<th>Time after surgery, wk:</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tr>
<td></td>
<td>Injured</td>
<td>Intact</td>
<td>Injured</td>
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<tr>
<td></td>
<td>RMT (% of maximum output)</td>
<td>AMT (% of maximum output)</td>
<td>MEP latency at rest, ms</td>
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<td>Pre</td>
<td>38.0</td>
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<td>100</td>
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APB, abductor pollicis brevis; RMT, rest motor threshold; AMT, active motor threshold; MEP, motor evoked potential; SICI, short-interval intracortical inhibition.
Intracortical facilitation

Figure 3B shows the findings for active SICI. ANOVA showed a main effect of time \( F(3,27) = 7.89, P < 0.001 \) on SICI for Patient 1, but the effect of side (injured vs. intact) and the interaction between time and side were not significant. For Patients 2 and 3, neither effect of side or time nor the side and time interaction were not significant. Different results showed that for Patient 1, there was no significant main effect of side and interaction between side and time were not. For Patients 2 and 3, neither effect of side or time nor the side and time interaction were not.

Intracortical facilitation

Figure 4A shows the findings for ICF at rest. ANOVA showed that for Patient 1, there was no significant main effect of side, time, or side and time interaction. Different results were obtained from Patient 2. ANOVA showed significant effect of side \( F(1,36) = 6.21, P = 0.034 \) and time \( F(1,36) = 2.78, P = 0.041 \), and significant side and time interaction \( F(1,36) = 7.43, P < 0.001 \). Post hoc tests showed higher ICF on the intact compared with the injured side before surgery \( (P < 0.01) \). For Patient 3, the effects of time was significant \( F(1,32) = 5.18, P = 0.006 \), whereas the main effect of side and the interaction between side and time were not.

Figure 4B shows the findings for active ICF. ANOVA shows that for Patient 1, there was no significant effect of side, time, or their interaction. In Patient 2, the effect of time \( F(1,36) = 3.31, P = 0.021 \) and interaction between side and time \( F(1,36) = 3.27, P = 0.027 \) were significant, but the effect of side was not. In Patient 3, there was no significant effect of side, time, or their interaction.

Relationship between physiological and clinical measures

We further examined the relationship between physiological measures (ratio of injured side to intact side for RMT and SICI) and clinical measures (key pinch and SWM for the injured thumb after surgery). The results are shown in Table 3. Figure 5 shows that the motor function (key pinch strength) on the injured side in Patients 1 and 2 significantly correlated with the RMT and SICI. Sensory function (SWM) of the reconstructed thumb also significantly correlated with the RMT and SICI. Patient 3 with immediately replanted thumb showed no significant correlation between physiological and clinical measures.

DISCUSSION

We had the unique and rare opportunity to examine how M1 excitability changes over time in two patients following thumb reconstruction using toe-to-thumb transfer 9–10 mo after amputation and in one patient following immediate thumb replantation. The findings on the injured side of the patients with toe-to-thumb transfer can be summarized as follows. 1) RMT and intensity for 1-mV MEP were decreased compared with the intact side before surgery and increased with time after surgery, whereas AMT did not change. 2) The rest and active MEP latencies were similar on the injured side before surgery and for \( \leq 15 \) wk after surgery, followed by restoration of the expected latency differences. 3) SICI was reduced before surgery and showed normalization with the time of recovery.
4) The recovery of motor and sensory functions was correlated with RMT and SICI. All measurements on the intact side and in the patient with immediate thumb replantation were stable over time.

Motor threshold

RMT reflects the excitability of the corticospinal pathway, including the cortical inhibitory or excitatory interneurons, corticospinal neurons, and spinal motoneurons (Rothwell 1997; Weber and Eisen 2002). In the present study, the RMT on the injured side of patients with late toe-to-thumb transfer was lower than the RMT on the intact side before surgery and increased with the time after surgery together with recovery of motor and sensory functions. Several lines of evidence suggest that this change in RMT was due to the reversal of reorganization occurring at the cortical level. First, in subjects with lower-limb amputation, RMT for the stump muscle elicited by TMS was reduced compared with the intact side, whereas RMT elicited by transcranial electrical stimulation (TES) was similar to that on the intact side (Chen et al. 1998a). Since TES activates corticospinal axons directly and is not sensitive to changes in cortical excitability, the decreased motor threshold from TMS after amputation is likely due to increased cortical rather than spinal excitability. Second, SICI, which reflects activity in a cortical inhibitory circuit, was also decreased after thumb amputation and increased with time after toe-to-thumb surgery. Third, studies with transient deafferentation showed that the reversible plastic changes in this setting were attributed to cortical mechanisms (Brasil-Neto et al. 1993; Ziemann et al. 1998b). Additionally, we found that the intensity to elicit 1-mV MEP at rest also increases with the time of recovery. RMT represents the excitability of the neurons most sensitive to TMS at the center of muscle representation. Higher intensity may activate neurons less sensitive to TMS or further from the center (Hallett 2007). Our findings indicate that not only the neurons at the center of the muscle representation but also those further from the center have increased excitability after amputation and this increased excitability may return to baseline after reconstruction of the amputated body part. This result confirmed the reversal of amputation-caused reorganization in the M1 with the reafferentation of the reconstructed thumb. In addition, it was found that AMT did not change over time, suggesting that the excitability of corticospinal neurons during voluntary contraction is not affected by amputation or the reafferentation of the lost body part. This is similar to the finding in free-functioning muscle transfer where there was reduction in RMT but no change in AMT (Chen et al. 2003). Since the corticospinal excitability is higher in the active condition than that at rest, it may be inferred that deafferentation caused by amputation elevates the resting corticospinal excitability toward that of the active state. In the active state the excitability is already adjusted to that required for appro-

TABLE 3. Results of Pearson’s correlation coefficient between physiological and clinical measures in Patients 1 and 2 with toe-to-thumb transfer and in Patient 3 with replantation of thumb

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tr>
<td><strong>R²</strong></td>
<td><strong>F</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Key pinch (motor function)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMT</td>
<td>0.99</td>
<td>330.81</td>
</tr>
<tr>
<td>SICI</td>
<td>1.00</td>
<td>1,123.41</td>
</tr>
<tr>
<td>SWM (sensory function)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMT</td>
<td>1.00</td>
<td>505.30</td>
</tr>
<tr>
<td>SICI</td>
<td>1.00</td>
<td>206.03</td>
</tr>
</tbody>
</table>

n.s., not significant; RMT, rest motor threshold; SICI, short-interval intracortical inhibition; SWM, Semmes–Weinstein monofilament.
appropriate muscle activation and deafferentation does not further increase the excitability.

**MEP latency**

The present study first reported that cortical plasticity may be associated with changes in MEP latency. If TMS is applied at rest, spinal motoneurons require summation of multiple descending indirect (I) waves to depolarize their membrane potential to the threshold level. Therefore MEP latency is related to the I2 or I3 wave. Voluntary muscle contraction raises the excitability of these spinal motoneurons and only one I wave (probably the I1 wave) may discharge them, leading to the shorter latency during voluntary muscle contraction compared with that at rest (Ni et al. 2007; Rothwell 1997; Weber and Eisen 2002). Our finding that MEP latencies at rest are about 2 ms longer than those during muscle activation on the intact side is consistent with previous reports. However, MEP latencies on the injured side of Patients 1 and 2 with toe-to-thumb transfer before and shortly after surgery were the same (Table 2) in both the rest and the active conditions. The shortened latency at rest may be explained by the higher excitability of the corticospinal neurons caused by amputation such that TMS can activate more corticospinal neurons and produce more I1 waves. The increased amount of I1 waves may discharge the spinal motoneurons and shorten the MEP latency at rest. An alternative explanation is that direct (D) waves may be generated with increased excitability of the corticospinal neurons after amputation. The summation of D and I1 waves was sufficient to discharge the spinal motoneurons, leading to the shortened MEP latencies. In a previous study, a patient with peripheral nerve injury showed a D wave evoked by TMS that was suppressed by long-interval intracortical inhibition (Chen et al. 1999). Therefore in some settings of cortical reorganization the D wave may become easier to evoke. It could arise from the sites closer to the initial segment and be more susceptible to cortical facilitatory and inhibitory processes than D waves evoked under normal circumstances. With recovery of motor and sensory functions, the difference in rest and active MEP latencies returned to the same level as that on the intact side, indicating that the increased excitability of the corticospinal neuron is reversed by the reafferentation of the amputated body part. Additionally, the result in Patient 3 with thumb replantation immediately after amputation showed no difference in MEP latencies on the injured and intact sides. This result suggested that the abnormal MEP latencies in Patients 1 and 2 were due to the cortical reorganization in M1 caused by the 9 to 10 mo of deafferentation and were reversed by the reconstruction of the lost body part.

**Intracortical inhibitory and facilitatory circuits in the primary motor cortex**

Besides the finding that the increased corticospinal excitability after thumb amputation is reversible by the reconstruction of thumb, we also found changes in intracortical circuits during the recovery period. Previous studies showed that SICI is due to cortical inhibition (Di Lazzaro et al. 1998; Kujirai et al. 1993). Other studies suggested that SICI at ISIs ≥2 ms is due to the synaptic inhibition in M1 mediated by GABA_A receptors (Fisher et al. 2002; Roshan et al. 2003; Ziemann et al. 1996a,b). In patients with above or below knee amputation, it was reported that SICI was decreased or abolished in the quadriceps muscle just proximal to the amputation, suggesting that the excitability of GABA_A-mediated inhibitory interneurons was reduced in the deafferented M1 (Chen et al. 1998a).
Our finding that SICI at rest was weaker on the injured side than on the intact side before and soon after surgery in the patients with late toe-to-thumb transfer is consistent with this study. One of the more important findings presented in this study was that the reduced SICI in the injured side can be reversed by the reafferentation after the thumb reconstruction. This finding suggests that not only the increased excitability of the corticospinal system but also that of the GABA$_A$-mediated inhibitory circuits are reversible. SICI did not change in Patient 3 on the injured or the intact side, suggesting that either the changes in cortical inhibition did not occur because of the short duration of amputation or it was quickly reversed after replantation of the thumb, and the changes after surgery in the patients with late toe-to-thumb transfer cannot be accounted for by the effects of the surgery itself. It was reported that SICI is a complex measure and may be contaminated by short-interval intracortical facilitation (SICF) (Ni and Chen 2008; Ortu et al. 2008; Peurala et al. 2008). However, two lines of evidence support that the reduced SICI before and shortly after surgery in Patients 1 and 2 is unlikely caused by the contamination of SICF. First, SICF occurs at ISIs of about 1.5, 2.9, and 4.5 ms (Chen and Garg 2000; Ziemann et al. 1998c) and the ISI of 2 ms used in the present study is at the trough of SICF where no significant facilitation would occur. Second, the same experimental protocol was performed on the intact side and at the later times of recovery on the injured side where significant SICI was found. Additionally, it should be noted that, similar to MEP threshold, SICI has large within-subject and between-subject variations (Wassermann 2002), in that it was found that SICI was significantly different on different experiment days for Patient 1 but not for Patients 2 and 3. We did not find different SICIs between injured and intact sides in the active state. This is likely because SICI is reduced during voluntary contraction (Hanajima et al. 2002; Ridding et al. 1995) compared with that at rest because reduced cortical inhibition during voluntary contraction may be required to allow ongoing muscle activity. Reduced SICI may be a compensatory mechanism after amputation to allow faster increase in cortical excitability to the active level, although a further increase in excitability is not required during the active state. This is consistent with decreased RMT but normal AMT after amputation.

We also examined how ICF changes during the time course of recovery. ICF is mediated by neuronal population separate from SICI since ICF and SICI are associated with different patterns of cerebral blood flow response (Strafla and Paas 2001) and they involve different neural transmitters (Ziemann et al. 1996c). We found that ICF was similar for the injured and intact sides for Patients 1 and 2, except for reduced ICF on the injured side in Patient 2 before surgery. Therefore the reduced SICI on the injured side for Patients 1 and 2 cannot be explained by changes in ICF. The mechanisms responsible for ICF may be complex. Although cortical facilitatory interneurons are thought to be involved (Kujirai et al. 1993; Ziemann et al. 1996c), ICF was not associated with an increase in descending corticospinal volleys (Di Lazzaro et al. 2006). Therefore ICF may be mediated by multiple mechanisms and include facilitation at both cortical and spinal levels, which may explain why ICF remains unchanged during the time course of recovery.

**Relationship between physiological and clinical measures**

The present study is the first to examine the relationship between physiological and clinical measures following reconstruction of amputated body parts. Although we studied only several time points after surgery, we found that the recovery of motor (e.g., key pinch) and sensory (e.g., SWM) functions was highly correlated to the measures in corticospinal excitability (RMT) and cortical inhibition (SICI). These results suggest that the changes in the corticospinal pathway (RMT) and intracortical circuits (SICI) may be an index for the functional recovery. However, the correlation analysis showed some unusual results, such as $R^2$ values close to 1 (Table 3). This is likely explained by the small number of data points used for the analysis. In addition, whether functional recovery is causing the reversal of cortical reorganization or vice versa requires further study.

**Comparison with cortical reorganization in other clinical settings**

It was reported that phantom pain is associated with the displacement of muscle representations adjacent to the amputated body parts (Karl et al. 2001), suggesting that this type of plasticity may be maladaptive. A TMS study showed reduced RMT and SICI measured in a functioning muscle after free-functioning muscle transfer, suggesting that some types of plasticity may be beneficial (Chen et al. 2003). A study in patients with immediate replantation of the hand after complete hand amputation showed similar MEP threshold and latencies on the injured and intact sides (Roricht et al. 2001), compatible with our findings in the patient with immediate thumb replantation. However, TMS mapping showed that the center of gravity of biceps muscle in the M1 expands toward the hand area by about 1 cm and this brain plasticity lasted for a long period (1–14 yr) after the hand replantation. In our patients, thumb amputation was not associated with muscle loss. In addition, the sensory and motor representations of the thumb were close to the representations of the other fingers and the thenar eminence was still intact. Even if there were a shift of the APB muscle representation, it would still be within the cortical hand area. Hot spot measurements are unlikely to have enough spatial resolution to detect the differences and we did not perform hot-spot measurements in the present study. Detailed TMS mapping with measurement of the center of gravity may be more sensitive in detecting such differences (Schabrun and Ridding 2007).

Although the significance of the reorganization in M1 that follows amputation is not fully known, enhanced function of the representation for the intact area surrounding the amputated body part has been reported (Chen et al. 2002). Our patients did not have muscle loss after thumb amputation, which is different from that of amputations at the level of the knee, elbow, or wrist. Therefore the absence of sensory afferentation from the lost thumb rather than the shift of muscle representation in the M1 played a major role in the cortical reorganization in our patients. Our finding that both RMT and SICI decrease after amputation suggests that chronic deafferentation leads to pronounced functional changes in the M1 (Chen et al. 1998a). Deafferentation may reduce the GABA$_A$-mediated SICI, leading to disinhibition of corticospinal neurons, which may induce
the cortical reorganization in the deafferented M1. This reorganization is reversed with reafferentation. In conclusion, our findings showed that cortical reorganization after traumatic thumb amputation can be reversed by reconstruction of the thumb and that plastic changes are highly correlated with restoration of thumb motor and sensory function.

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