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Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke

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Summary

Following a hemispheric stroke, various degrees of neuronal reorganization around the lesion occur immediately after disease onset and thereafter up to several months. These include transcallosal excitability, changes of the intact motor cortex and ipsilateral motor responses after transcranial magnetic stimulation (TMS) on the intact hemisphere. To elucidate the relationship between lesion localization and motor cortex excitability (intracortical inhibition; ICI) in the intact hemisphere, we applied a paired conditioning-test TMS paradigm in 12 patients with unilateral cortical stroke (cortical group) and nine patients with subcortical stroke caudal to the corpus callosum (subcortical group), with interstimulus intervals varying from 1 to 10 ms. All patients exhibited unilateral complete hand palsy. ICI was significantly less in the cortical group than in age-matched healthy control subjects. It was especially more marked in the cortical group patients with a disease duration of less than 4 months after onset. Patients in the cortical group with a duration longer than 4 months showed a tendency for ICI to be normalized, and there was a significant correlation between ICI and disease duration. Patients in the subcortical group showed normal excitability curves. All patients in the cortical group showed no transcallosal inhibition (TCI) in the active unaffected hand muscle after TMS of the affected motor cortex, whereas all the subcortical patients showed some TCI. No ipsilateral motor responses were elicited in the paretic hand in any of the patients. The reduced ICI in the cortical group might have been a result of disruption of TCI. The normalization of ICI in the patients with longer disease duration and the normal ICI in the subcortical group patients do not support the functional significance of motor cortex hyperexcitability in the unaffected hemisphere, at least in a patient population with poor motor recovery.

Keywords: stroke; unaffected hemisphere; transcranial magnetic stimulation; intracortical inhibition; transcallosal inhibition

Abbreviations: AT = active motor threshold; FDI = first dorsal interosseous; ICI = intracortical inhibition; ISI = interstimulus interval; MEP = motor evoked potential; TCI = transcallosal inhibition; TMS = transcranial magnetic stimulation

Introduction

Stroke, an acute localized brain lesion of vascular origin, potentially alters neuronal function of areas adjacent to or distant from the lesion through neuronal networks. After a stroke affecting the subcortical motor pathway, the excitability motor threshold is increased on the affected side (Byrnes *et al*., 1999) and motor output areas are decreased (Cicinelli *et al*., 1997*b*; Traversa *et al*., 1997; Liepert *et al*., 2000*a*). In the recovery stage after stroke, neuronal reorganization is often induced, such as enlargement of the motor cortical representation, shift of the motor spot on the affected hemisphere, enhanced activation of secondary motor areas, and anomalous motor representations for the paretic hands (Chollet *et al*., 1991; Weiller *et al*., 1992, 1993; Cicinelli *et al*., 1997*b*; Traversa *et al*., 1997; Rossini *et al*., 1998;

Byrnes *et al*., 1999; Cramer *et al*., 2000; Marshall *et al*., 2000). The motor cortex rostral to the subcortical stroke lesions may show a decrease in intracortical inhibition (ICI) (Liepert *et al*., 2000*c*). Ipsilateral motor responses after transcranial magnetic stimulation (TMS) on the unaffected hemisphere occasionally emerge as lesion-induced central reorganization (Caramia *et al*., 1996, 2000; Turton *et al*., 1996; Netz *et al*., 1997; Trompetto *et al*., 2000). Severe motor cortex damage modifies transcallosal inhibition (TCI) (Boroojerdi *et al*., 1996) and hyperexcitability of the unaffected motor cortex might occur, as reflected by a larger than normal motor response size from intact hands (Cicinelli *et al*., 1997*b*; Traversa *et al*., 1997, 1998; Liepert *et al*., 2000*a*, *b*).

Some of the neuroplastic changes after stroke are helpful for the recovery of functional deficits, but other changes might be aberrant or non-purposeful for recovery, or their roles remain to be elucidated. The significance of ipsilateral motor responses from the unaffected hemisphere for motor recovery has been considered to be doubtful (Palmer *et al*., 1992; Turton *et al*., 1996; Netz *et al*., 1997), since the ipsilateral corticospinal fibres represent less than 10% of the motor cortex output, the majority of which ultimately crosses within the segmental cord (Porter and Lemon, 1993; Rouiller, 1996). Moreover, the function of motor cortical hyperexcitability in the unaffected hemisphere of stroke patients is unclear. Whether this hyperexcitability has a beneficial or poor effect on recovery of the plegic hands remains unknown. Furthermore, there have been no studies on the relationship between the hyperexcitability in the unaffected hemisphere and the location of the lesion. If the hyperexcitability is a result of disruption of transcallosal modulation, patients with stroke lesions caudal to the corpus callosum would show normal intracortical motor inhibition or facilitation in the unaffected hemisphere, while patients with cortical lesions should display abnormalities of ICI and TCI for the intact motor cortex.

In the present study, we investigated the excitability of the unaffected motor cortex in stroke patients with unilateral cortical or subcortical stroke to elucidate its relation to the location of the lesion and to clarify the functional significance of the ipsilateral motor cortical disinhibition. We focused on one hand muscle of the intact side, since hand muscles are less controlled by the ipsilateral motor cortex in healthy people and are most severely affected by monohemispheric stroke.

Patients and methods

Subjects

In total, 21 hemiparetic patients with stroke (mean age 63.7 $\pm$ 7.6 years, range 50–74 years; seven women and 14 men) participated in the study. Criteria for their inclusion were (i) first-ever attack; (ii) brain CT or MRI demonstrating a single vascular lesion; (iii) the affected hand being completely paretic at the time of investigation (–4 in grading of muscle strength and weakness according to the scheme described by the Mayo Clinic and Mayo Foundation, 1998); and (iv) age below 75 years. All patients were right-handed. We carefully selected patients who were completely paretic in their hand and finger movements, so as to ensure that TMS on the hemisphere contralateral to the paretic limb elicited no motor responses from the affected first dorsal interosseous (FDI) muscle. The ability to extend or flex the elbow of the paretic arm, weakness of the paretic leg and Babinski's sign varied among the patients (Table 1). The unaffected upper and lower limbs showed no obvious weakness, spasticity, ataxia or clumsiness in any patients. There were no patients who showed mirror hand movements. Exclusion criteria were concomitant neuropathies, systemic vasculopathies, dementia and severe aphasia that made the patient uncooperative. No patients were taking drugs that could affect the excitability of the motor cortex, such as anti-epileptic and psychoactive drugs.

The patients were classified into the following two subgroups according to brain CT or MRI findings: (i) a cortical group, who had stroke lesions involving the unilateral sensorimotor cortex (referred to as the 'total cortical group' in the following text; 12 patients, age range 52–74 years, mean age 62.1 years); and (ii) a subcortical group, who had lesions located caudal to the corpus callosum (nine patients, age range 50–74 years, mean age 65.9 years), indicating that the corpus callosum was intact. The causes of stroke are listed in Table 1. The patients in the cortical group had a middle cerebral artery embolism or atheromatous occlusion of the internal carotid artery. In the subcortical group, the causes were middle cerebral artery thrombosis sparing the cortex; lacunar stroke affecting the internal capsule; hypertensive capsular haemorrhage; or brainstem infarction due to basilar or vestibular artery sclerosis. We carefully excluded patients with lesions in the corona radiata since such lesions often overlapped areas rostral and caudal to the corpus callosum.

The patients in the cortical group were further classified arbitrarily into an 'early cortical group' (eight patients, mean age 64.3 years; Patients 1–8) and a 'late cortical group' (four patients, mean age 57.8 years; Patients 9–12) according to the interval between disease onset and the time of examination (Table 1). The intervals in the early and late cortical groups were less (0.6–2.9 months) and more (5.4–12.9 months) than 4 months, respectively. The aim of the comparison between the early and late cortical groups was to study the possibility of long-term reorganization of the motor cortex for the unaffected hand. For stroke patients, our institute is specialized only for treatment in an acute stage, and long-term follow-up of individual stroke patients is not possible. Therefore, comparison between the two groups at different stages was the only way for us to investigate long-term neuroplastic changes after a stroke. The interval between disease onset and time of examination in the subcortical group was less than 4 months (0.5–2.8 months) in all cases.

Table 1 *Patient details*

Patient	Gender	Age (years)	Disease duration (months)	Diagnosis	Paretic side	Weakness of proximal arm	Weakness of lower limb	Spasticity or brisk reflexes	Babinski's sign	Hemisensory disturbance
Cortical group										
1	M	53	0.6	MCA embolism	Right	Moderate	Moderate	–	+	+
2	F	74	1.1	ICA occlusion	Right	Moderate	Moderate	–	+	–
3	M	68	1.1	MCA embolism	Right	Marked	Marked	+	–	+
4	M	67	2.0	MCA embolism	Left	Marked	Marked	+	+	–
5	M	59	2.0	MCA embolism	Right	Moderate	Moderate	+	+	+
6	M	62	2.1	ICA occlusion	Left	Marked	Marked	+	+	+
7	M	64	2.3	MCA embolism	Right	Marked	Marked	–	+	+
8	M	67	2.9	MCA embolism	Right	Marked	Marked	+	–	+
9	M	65	5.4	MCA embolism	Right	Marked	Mild	+	+	+
10	M	55	5.5	MCA embolism	Left	Marked	Mild	+	+	+
11	F	52	8.0	MCA and ACA occlusion	Right	Moderate	Mild	+	–	+
12	M	59	12.9	MCA embolism	Left	Marked	Mild	+	+	+
Subcortical group										
13	F	74	0.5	Pontine base infarction	Right	Moderate	Moderate	+	–	–
14	M	70	0.6	MCA thrombosis	Left	Mild	Mild	–	–	+
15	M	50	1.3	Capsular haemorrhage	Right	Moderate	Mild	+	–	+
16	M	72	1.4	MCA thrombosis	Left	Mild	Mild	+	–	–
17	F	76	1.9	Pontine base infarction	Right	Moderate	Mild	+	+	–
18	F	69	2.2	Capsular haemorrhage	Left	Moderate	Moderate	+	–	+
19	F	60	2.5	MCA thrombosis	Left	Marked	Marked	+	+	+
20	F	68	2.8	Medullary infarction	Left	Marked	Marked	+	+	+
21	M	55	2.8	MCA thrombosis	Left	Marked	Moderate	+	+	+

M = male; F = female; MCA = middle cerebral artery; ICA = internal carotid artery; ACA = anterior cerebral artery.

Table 2 *TMS data for individual patients*

Patient	Active threshold (%)	MEP amplitudes after paired-pulse TMS at each ISI (% of control MEP)					
		1 ms	2 ms	3 ms	5 ms	7 ms	10 ms
Cortical group							
1	56	64	94	89	82	165	127
2	40	54	111	94	93	81	107
3	42	15	81	80	86	123	131
4	40	117	98	131	123	148	117
5	64	32	26	19	38	92	145
6	48	11	92	82	123	111	140
7	44	80	53	90	83	211	115
8	46	40	99	95	109	203	213
9	41	18	19	33	79	95	96
10	52	12	74	74	75	92	92
11	52	7	13	27	59	128	98
12	50	2	13	2	51	82	106
Subcortical group							
13	46	3	16	26	43	109	139
14	32	27	42	42	85	96	123
15	40	16	41	62	97	110	132
16	42	6	8	16	7	111	142
17	46	7	17	15	59	127	180
18	52	19	39	39	90	96	106
19	40	10	32	32	83	113	117
20	52	25	18	36	39	98	111
21	52	27	18	15	78	111	117

Ten healthy, right-handed, age-matched control subjects (four women and six men, age range 45–68 years, mean age 58.0 years) were also investigated for comparison. All patients and control subjects gave their written informed consent to the study. The experimental procedures were approved by the Tokyo Metropolitan Neurological Hospital Ethics Committee.

Procedures

Patients and subjects were seated on a comfortable reclining chair. Surface EMG was recorded from the FDI muscle in the unaffected hand in patients and in the left hand in control subjects, using disc electrodes (Ag–AgCl) attached in a belly tendon montage. Responses were amplified and filtered through a Counterpoint electromyograph (Dantec, Skovlunde, Denmark) with the band-pass ranging from 10 Hz to 1.5 kHz, a sweep time of 500 ms and a sampling rate of 5 kHz. Measurements were inspected on-line and stored on the hard drive of an IBM-compatible computer for off-line analysis. Focal TMS was applied through a figure-of-eight coil (diameter of each wing 70 mm) using Magstim 200 magnetic stimulators (Magstim, Whitland, UK). In all TMS procedures, the intertrial interval was >5 s.

MEPs from the paretic hands

First, we examined whether the focal TMS on the affected hemisphere elicited motor evoked potentials (MEPs) in the contralateral paretic FDI muscle in the patients. For this purpose, the stimulus intensity was set at 100% of the output of the single Magstim 200, and MEPs were recorded from the affected FDI while the patient remained relaxed and when he or she tried to contract the paretic hand as strongly as possible. The stimulation site was searched on the scalp around the presumed motor cortex, which was approximately symmetrical to the opposite motor cortex, contralateral to the intact hand. The handle of the coil was directed posteriorly and 45° away from the parasagittal line to induce maximal MEP responses.

Intracortical inhibition

Intracortical excitability of the unaffected motor cortex was studied by a paired conditioning–test stimulation paradigm (Kujirai *et al*., 1993; Ziemann *et al*., 1996; Shimizu *et al*., 1999). For this purpose, two magnetic stimulators were connected to one coil through a Bistim device (Magstim). The coil was placed tangentially to the scalp contralateral to the unaffected FDI in patients or the left FDI in control subjects, with the handle pointing backwards in the parasagittal line. The optimal position of the coil was the scalp site where the largest MEP could be obtained from the contralateral target FDI muscle (this was the unaffected FDI in patients). This site was marked with a red pencil to ensure a constant position of the coil relative to the scalp throughout the recording session. The active threshold (AT) was determined in the tonically active FDI muscle as the minimum stimulation intensity (%)

that evoked a clearly distinguishable MEP from the background EMG. In determining the AT, the subjects were requested to contract the FDI muscle as slightly as possible. During this procedure, the second magnetic stimulator remained in standby mode because the Bistim module leads to some reduction in the peak magnetic field. For paired TMS, the conditioning stimulus was applied to the same stimulating coil as the test stimulus at given interstimulus intervals (ISIs). The intensity of the conditioning stimulus was at the submotor threshold (5% of the stimulator output below AT). The test stimulus intensity was adjusted in intensity to produce a control MEP of ~0.5–1 mV in peak-to-peak amplitude. Any effect of the conditioning stimulus on the size of the test MEP is thought to occur at a supraspinal, probably cortical level, because the conditioning stimulus has no effect on spinal motor neurone excitability as tested by H reflexes (Ziemann *et al*., 1996). During the examination, subjects were requested to keep their eyes open and not to get drowsy. Complete relaxation of the target muscle was monitored by visual and auditory feedback at high gain. ISIs were set at 1, 2, 3, 5, 7 and 10 ms. Non-conditioned (control) and conditioned test stimuli at different ISIs were intermixed randomly. We collected eight to 10 test responses that were conditioned and non-conditioned for each ISI, and measured their peak-to-peak amplitude. Thereafter, the amplitude of the conditioned response was expressed as a percentage of the control response (amplitude ratio). In addition, the sum of the percentages at ISI 1, 2 and 3 ms was calculated as an index of ICI for each subject.

Transcallosal inhibition

We also investigated the TCI of the tonic voluntary contraction of the FDI muscle (Meyer *et al*., 1995, 1998). Focal TMS was performed over the presumed hand motor area of the hemisphere contralateral to the affected hand in patients or of the left hemisphere in control subjects (both of which were the opposite hemisphere to those in the paired-pulse study), using a single Magstim 200 stimulator. Because TMS on the hemisphere contralateral to the affected hand did not provoke any visible MEPs in the patients, the stimulation position was determined as the symmetrical site to the opposite motor cortex contralateral to the unaffected hand, from the viewpoint of normally symmetrical organization of hemispheric motor output in healthy subjects (Cicinelli *et al*., 1997*b*). The coil was held tangentially to the scalp, with the handle pointing backwards and 45° away from the parasagittal line. Subjects were required to gently contract the unaffected FDI (patients) and the left FDI (controls), both of which were ipsilateral to the stimulated hemisphere, at ~50% of their maximal force, and the surface EMG was recorded. The muscle force was first determined with a pinch metre and monitored using a loudspeaker to maintain constant contraction. The stimulus intensity was set at 80% of the stimulator's maximum output. Eight magnetic stimuli were applied, and the decrease in the sustained tonic muscle activity to a value of approximately <50% of the mean amplitude was considered to reflect the effect of TCI.

Ipsilateral MEP

We investigated in the patients whether TMS on the motor cortex ipsilateral to the paretic hand produced MEPs from the affected FDI muscle. For this examination, the patients were requested to try to contract the affected FDI as strongly as possible, although there was no visible contraction of the paretic hand muscles. We did not instruct the patients to contract the intact hand. The stimulus intensity was 100% of the output. The orientation of the coil handle was backwards and 45° away from the parasagittal line. An averaging technique was not used. We did not stimulate the more frontal areas, such as the premotor cortex, to evoke the ipsilateral responses, but stimulated only the primary motor cortex contralateral to the intact hand.

Statistics

For statistical analysis of the changes in MEP amplitudes at each ISI in the paired-pulse study, we used factorial ANOVA (analysis of variance). We also used the Mann–Whitney *U*-test to compare the mean MEP amplitude ratio at each ISI and the sum of the amplitude ratio (ISI 1–3 ms) between the cortical and subcortical groups. The correlation between the sum of the amplitude ratio and the disease duration was analysed using linear regression and Spearman's rank correlation coefficient test. The *P* values for all data were two-sided, and the level of significance was set at 5%.

Results

MEPs from the paretic hands

TMS on the contralateral hemisphere to the paretic hands elicited no MEPs from the affected FDI either at rest or when attempts were made to contract the muscle in any of the patients in the cortical or subcortical groups.

Active motor threshold

The AT for the unaffected FDI muscle in patients or the left FDI in control subjects measured before the paired-pulse study was 44.2 ± 5.8% (mean ± SD) in the control group, 47.9 ± 7.3% in the cortical group and 44.7 ± 6.9% in the subcortical group; there was no significant difference between groups (Table 2).

Intracortical inhibition

Representative MEP waveforms and MEP amplitude ratio curves for the paired-pulse study are shown in Figs 1 and 2, respectively. The control group showed significant inhibition of the mean amplitude of the test MEP by the conditioning

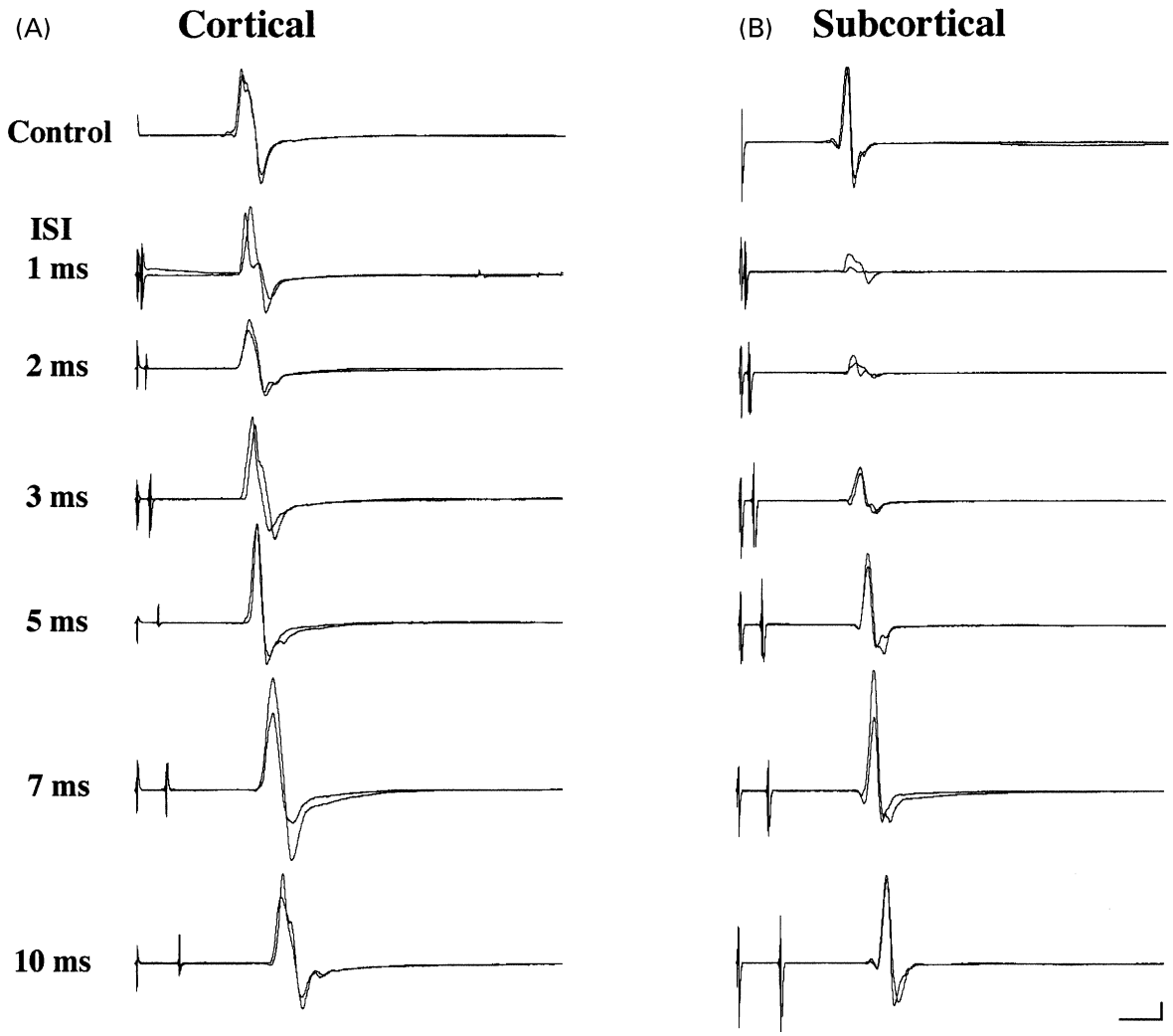

Fig. 1 Motor evoked potential (MEP) waveforms of the control (non-conditioned) and conditioned responses in representative patients in the cortical (**A**) and subcortical (**B**) groups. Two recordings are superimposed. The vertical and horizontal calibration bars represent 100 μV and 10 ms, respectively. Note the lack of ICI in the cortical group at ISIs of 1, 2 and 3 ms. ISI = interstimulus interval.

stimulus at ISIs of 1–5 ms ($P < 0.05$, ANOVA at each ISI) (Fig. 2). At an ISI of 7 ms, the excitability curve returned to the baseline, and at an ISI of 10 ms it showed non-significant facilitation. The cortical group showed clearly less inhibition than controls, or even facilitation in some individual patients, at ISIs of 1–3 ms, and significant facilitation at ISIs of 7 and 10 ms (Figs 1 and 2, Table 2). Statistical comparison with the findings in the control group showed significant differences (less inhibition) in the cortical group at ISIs of 1–3 ms ($P < 0.01$ at 1 ms, $P < 0.05$ at 2 and 3 ms; Mann–Whitney *U*-test) (Fig. 2). For the early cortical group alone, there was no significant inhibition at ISIs of 2 and 3 ms (ANOVA), and the difference from the control findings was more significant at short ISIs compared with the total cortical group ($P < 0.01$ at any of 1, 2 and 3 ms; Mann–Whitney *U*-test) (Fig. 2). In the late cortical group, Patient 10 showed a reduced inhibition pattern similar to the finding in the early cortical group, but the other three patients (Patients 9, 11 and 12) showed normal-appearing excitability curves (Fig. 3). The sums of the amplitude ratios at ISIs of 1–3 ms in the total cortical and early cortical groups were significantly greater than that in the control groups ($P < 0.05$ and $P < 0.01$, respectively; Mann–Whitney *U*-test) and also than that in the subcortical group ($P < 0.05$ and $P < 0.01$, respectively; Mann–Whitney *U*-test) (Fig. 4). The findings in the subcortical group were similar to those in the control group for both the inhibition and the facilitation phase (Figs 1–4). There were no significant differences in the amplitude ratio between the patients with right- and left-hand paresis in either patient group. The regression analysis between the sum of the amplitude ratios at ISI 1–3 ms and disease duration showed a significant correlation in the cortical group ($r = 0.7325$, $P < 0.05$, Spearman's rank correlation test) (Fig. 5). There was no significant correlation between the active threshold and the sum of the amplitude ratios in the patients or control subjects. The clinical variation among the patients in weakness of

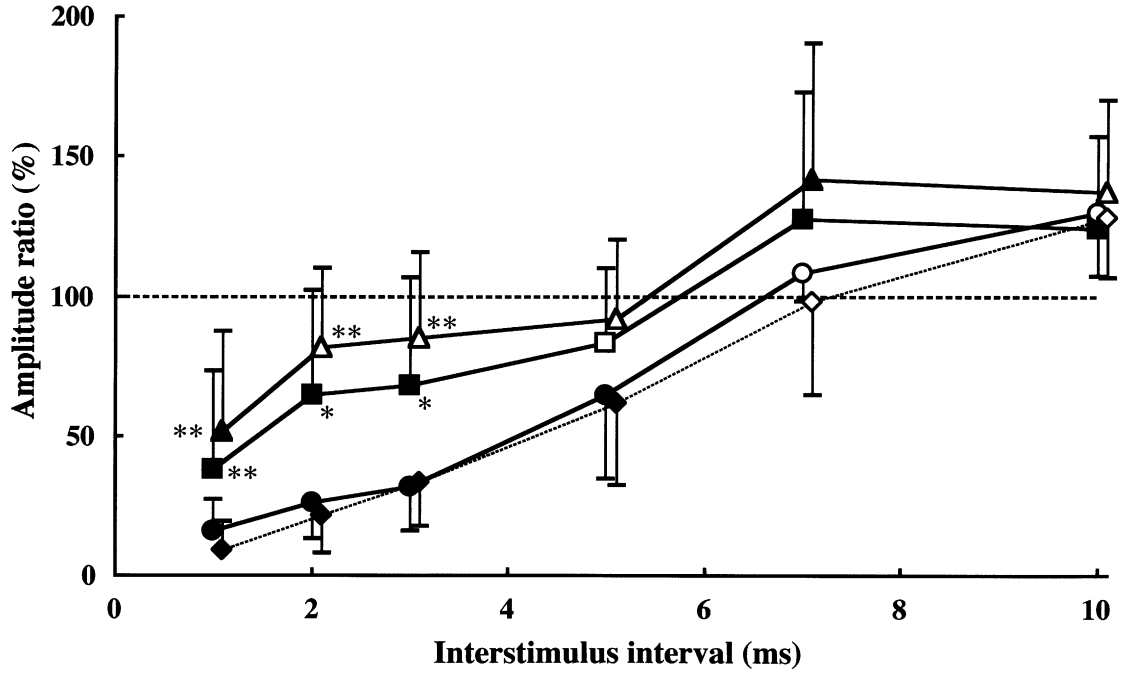

Fig. 2 Effect of subthreshold conditioning stimulation as the percentage ratio of the mean conditioned to non-conditioned motor evoked potential (MEP) amplitude in the cortical (early + late; squares), subcortical (circles) and control groups (diamonds). Triangles indicate the findings for the early cortical group. Values below 100% represent inhibition. Vertical bars represent the standard deviation. Closed symbols represent significant inhibition or facilitation at each interstimulus interval in each group (ANOVA, $P < 0.05$). *$P < 0.05$ and **$P < 0.01$ when the amplitude ratios were compared with those in the control group using the Mann–Whitney *U*-test. Control MEP amplitudes are represented by a horizontal dashed line.

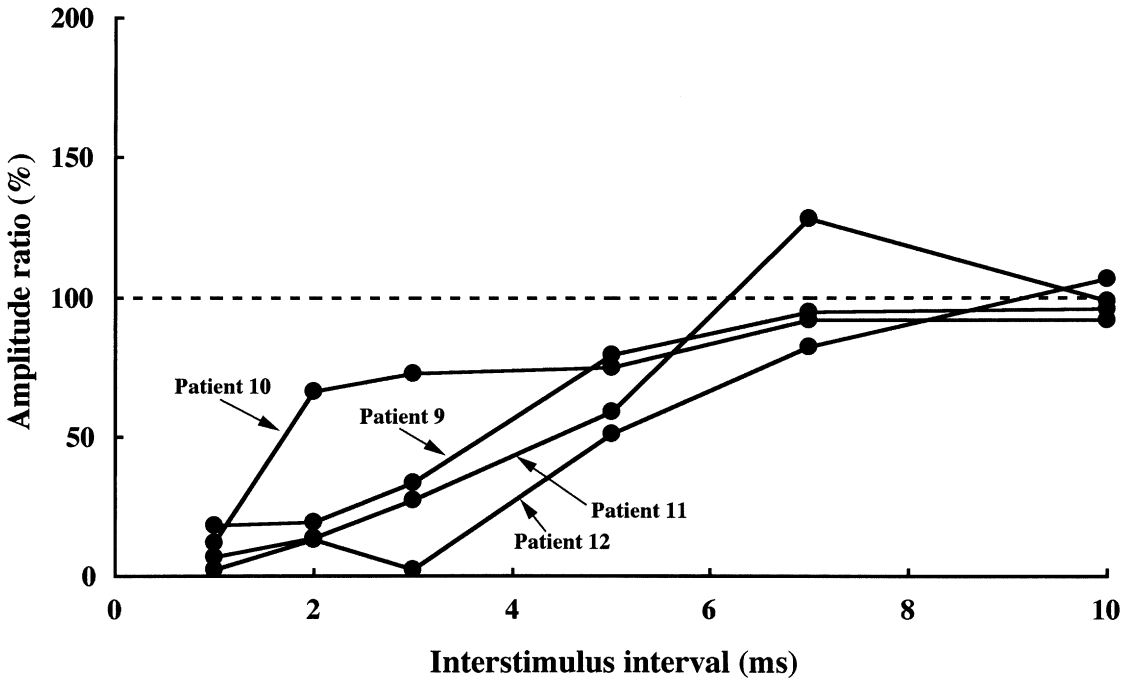

Fig. 3 Effect of subthreshold conditioning stimulation as the percentage ratio of the mean conditioned to non-conditioned motor evoked potential (MEP) amplitude in individual patients of the late cortical group (Patients 9–12). Values below 100% represent inhibition. Control MEP amplitudes are represented by a horizontal dashed line.

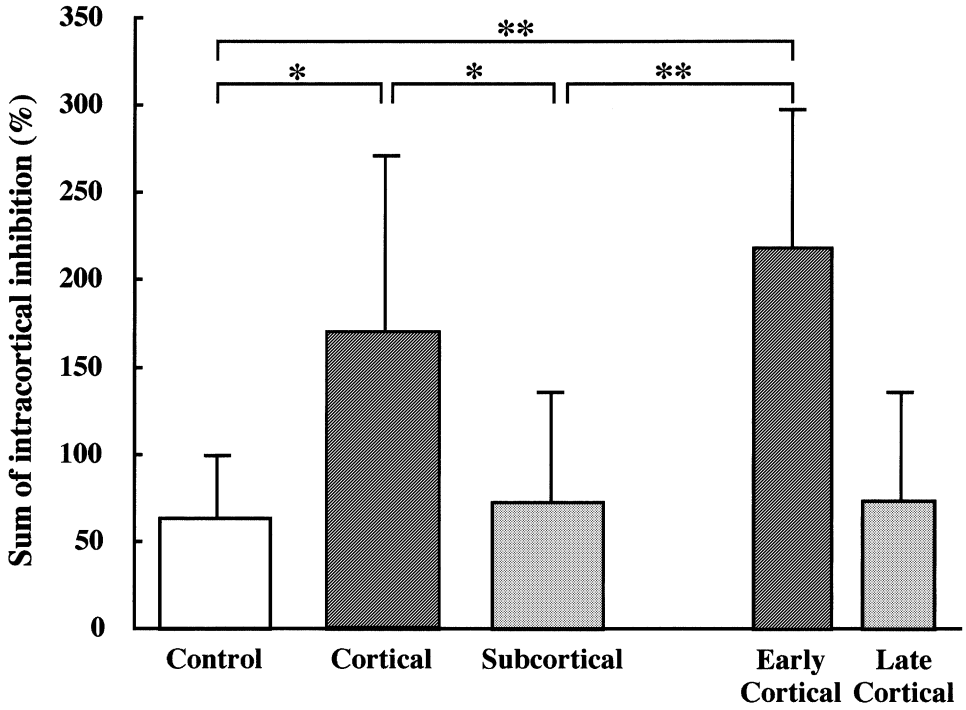

Fig. 4 Mean of the sum of the amplitude ratios (%) at interstimulus intervals of 1, 2 and 3 ms as an index of intracortical inhibition in the control, cortical, subcortical, early cortical and late cortical groups. Vertical bars represent the standard deviation. *$P < 0.05$; **$P < 0.01$.

proximal arms or legs, spasticity or deep tendon reflexes of the paretic limbs, Babinski's sign and hemisensory disturbance was not correlated with the ICI measurements.

Transcallosal inhibition

TMS on the hemisphere contralateral to the paretic hands produced no definite suppression of EMG activity in the ipsilateral unaffected FDI muscle in any of the cortical group patients, whereas all patients in the subcortical group showed clearly visible suppression of EMG activity (i.e. TCI) relative to the prestimulus background EMG levels, the onset latency of which was ~30–35 ms (Fig. 6). The result for a healthy control subject (a 40-year-old man) is also shown in Fig. 6 for comparison.

Ipsilateral MEP

No obvious ipsilateral MEPs were elicited from the affected FDI muscle in any of the patients in the cortical or subcortical groups.

Discussion

The present study clearly showed the ipsilateral motor cortical disinhibition during the early stage of stroke affecting the unilateral motor cortex. This phenomenon was accompanied by disruption of the TCI, and was not observed in patients with subcortical stroke caudal to the corpus callosum. These findings suggest that this ipsilateral motor cortical disinhibition might have been caused by disruption of the TCI after the contralateral cortical damage. Change in spinal excitability as a cause of the ipsilateral disinhibition is unlikely because, if the hand paresis (which was similar in the cortical and subcortical groups) had had some effect on the contralateral spinal motor neurones, such an effect would have produced similar excitability curves in the two groups. In fact, the intact arms and hands showed normal muscle tone in all patients in the cortical and subcortical groups. Several parameters have been used to assess the excitability of the motor cortex by TMS in general: resting and active motor thresholds; MEP amplitudes; cortical silent periods; TMS maps; MEP recruitment order; and intracortical inhibition or facilitation by a paired-pulse paradigm (Rossini *et al*., 1994; Pascual-Leone *et al*., 1998; Rossini and Rossi, 1998). Among these, the use of the paired-pulse method has been considered to be one of the most sensitive strategies to investigate motor cortex excitability. In some situations, it can detect an alteration in excitability even when there is no change in motor threshold. Also in the present study, the AT did not differ between the two groups, whereas there were marked differences in ICI.

The precise relation of TCI to ICI, i.e. whether the lack of TCI would release the upper motor neurones from inhibition by intracortical interneurones, or whether transcallosal neurones directly modulate the intracortical inhibitory

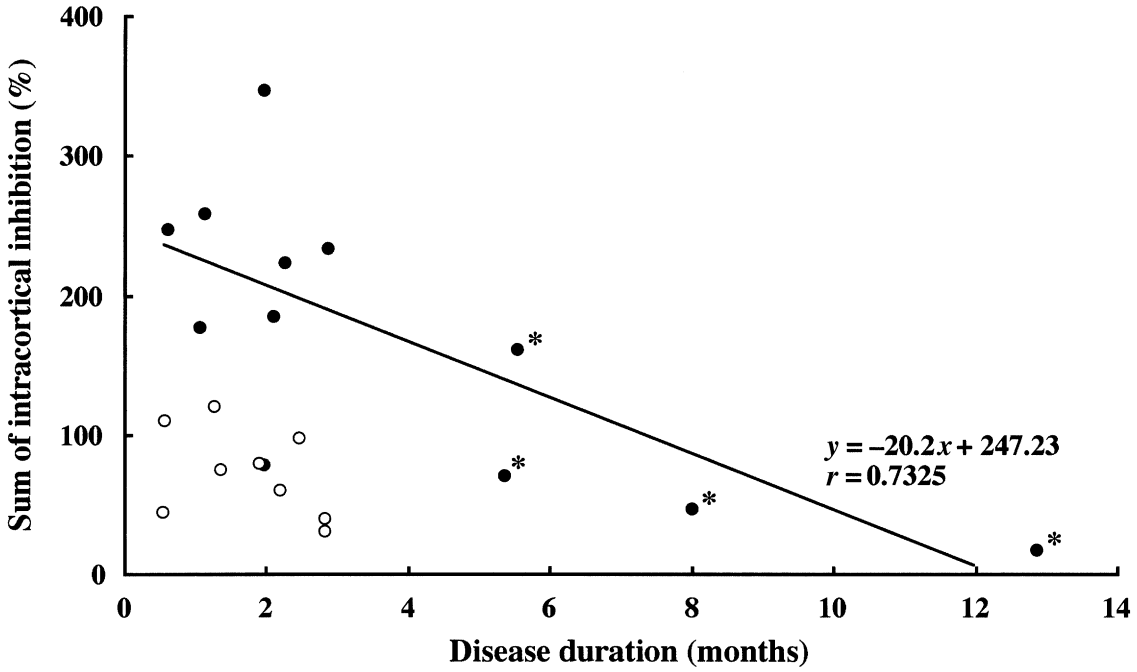

Fig. 5 Relationship between disease duration and the sum of the amplitude ratios (%) at interstimulus intervals of 1, 2 and 3 ms in the individual patients. Closed and open circles represent the cortical and subcortical group patients, respectively. The regression line drawn from the findings for the cortical group patients shows a significant correlation ($y = -20.2x + 247.2$; $r = 0.7325$, $P < 0.01$). Asterisks indicate the findings for the patients in the late cortical group.

interneurones that produce ICI, remains unknown. The present study suggests a close relationship—direct or indirect—between TCI and ICI, although we did not evaluate TCI quantitatively using a paired-pulse technique for relaxed muscles. Transcallosal modulation between the bilateral motor cortices, as investigated by TMS, includes both inhibition and facilitation (Ferbert *et al*., 1992; Ugawa *et al*., 1993; Meyer *et al*., 1995, 1998; Hanajima *et al*., 2001). Although the clinical significance of inhibition and facilitation has not been elucidated fully, detailed TMS studies have disclosed that transcallosal inhibition is more powerful and more easily detected than facilitation in humans (Hanajima *et al*., 2001). The disruption of TCI by unilateral motor cortex damage must clearly have induced neuroplastic reorganization of the contralateral motor cortex (Netz *et al*., 1997; Shimizu *et al*., 2000), which is consistent with previous animal studies. In rats, a lesion penetrating into deep cortical layers or including the complete territory of the middle cerebral artery induced hyperexcitability in the contralateral hemisphere; this might have been a result of down-regulation in GABA receptors and enhancement of glutamatergic activity (Buchkremer-Ratzmann *et al*., 1997; Que *et al*., 1999*a*, *b*; Reinecke *et al*., 1999).

During the rehabilitation period starting after stroke, use of the intact arm and hand tends to be enhanced in all daily activities, especially in patients with dominant hand paresis. ICI is modified in a task- and use-dependent manner (Liepert *et al*., 1998), and unilateral hand overuse itself might induce cortical hyperexcitability. However, this possibility is unlikely in the present patients since it would be unreasonable to assume that there were some differences in the amount of movement by the intact hand between the two groups, who showed similar degrees of hand paresis (Liepert *et al*., 2000*b*). The ipsilateral disinhibition should be interpreted not as a result of peripheral feedback but as a result of central reorganization after brain injury. Immobility of unilateral hand muscles induces alteration in the excitability of the contralateral motor cortex, presumably through sensory feedback, and this would be true in the subcortical group patients, who showed no sensory dysfunction (Patients 13, 16 and 17) (Zanette *et al*., 1997). This suggests that, even if the excitability alteration in the affected hemisphere does occur (Liepert *et al*., 2000*c*), the alteration would produce no or little effect on the excitability in the opposite motor cortex, ipsilateral to the affected hand, at least as tested with the present method.

There have been some previous reports in which hyperexcitability of the ipsilateral motor cortical was reflected as increased MEP size or enlarged cortical areas producing MEPs in the contralateral hand muscles in stroke (Cicinelli *et al*., 1997*b*; Traversa *et al*., 1997, 1998, 2000; Liepert *et al*., 2000*a*). These functional alterations in the unaffected motor cortex show chronological changes along with the disease course even up to 4 months after onset (Cicinelli *et al*., 1997*b*; Traversa *et al*., 1998, 2000). In fact, as the excitability in the affected motor cortex gradually

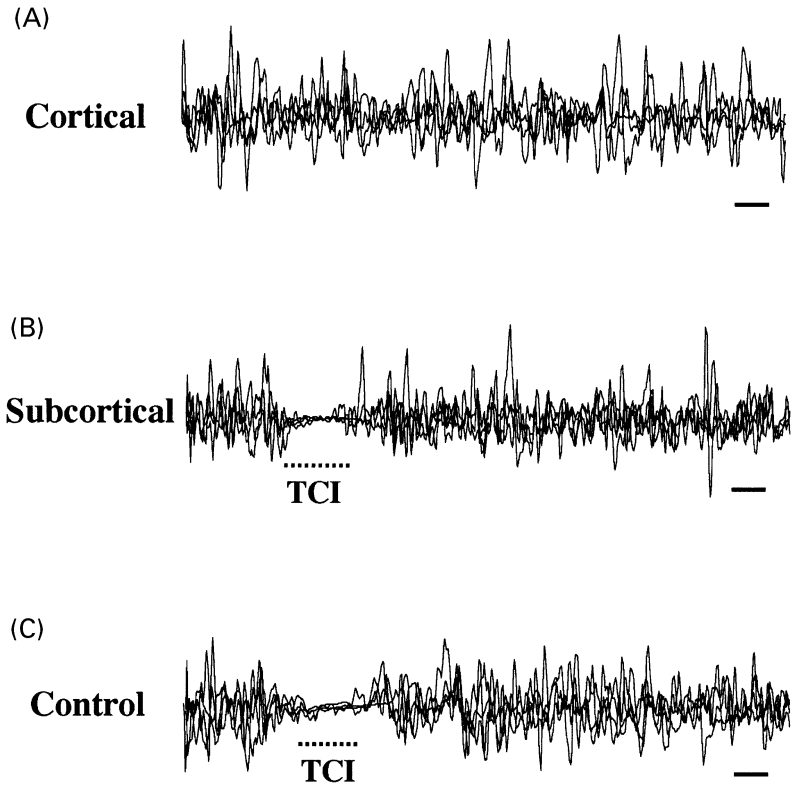

Fig. 6 Representative waveforms of EMG activity suppression in the unaffected first dorsal interosseous muscle after TMS on the estimated motor cortex of the affected hemisphere in the patients in the cortical (**A**) and subcortical groups (**B**). The waveform of a healthy control subject (40-year-old man) is shown for comparison (**C**). Four traces are superimposed. The horizontal calibration bars represent 10 ms. TCI = transcallosal inhibition.

recovers after stroke, the initially increased excitability in the intact motor cortex decreases; this is considered as a 'balancing phenomenon' mediated by transcallosal modulation between the two hemispheres. In stroke patients with poor motor recovery, this balancing phenomenon is occasionally lacking (Traversa *et al*., 1998). The precise function of the ipsilateral motor cortical hyperactivity remains to be clarified. The questions are whether it provides a beneficial, poor or no effect on motor recovery of the paretic hand, and whether the balancing phenomenon or recovery of the augmented ipsilateral excitability is a trigger for or a result of recovery of the affected motor cortex. Although we could not evaluate the chronological changes in individual patients, the normal ICI in three of four patients in the late cortical group, who also showed poor motor recovery, indicated that the ipsilateral disinhibition does not always last to the chronic stage. In addition, the normal ICI in the subcortical group patients, who were in the very early stage of disease, does not support the clinical significance of the balancing phenomenon, at least in a patient population with severe hand paresis due to complete destruction of the upper motor neurones.

Ipsilateral motor responses have been recorded from paretic hand muscles after stimulation of the unaffected motor cortex in stroke patients (Palmer *et al*., 1992; Caramia *et al*., 1996, 2000; Turton *et al*., 1996; Netz *et al*., 1997; Trompetto *et al*., 2000). Netz *et al*. (1997) reported that stroke patients with poor motor recovery of the hand showed ipsilateral MEPs from the paretic hand more frequently than patients with good recovery. These ipsilateral MEPs are ascribable to the unmasking or disinhibition of the ipsilateral corticospinal tract by lack of inhibition from the affected motor cortex. In the present study, no patients, even in the early cortical group, showed ipsilateral responses. The reason for this discrepancy is unknown, but one possibility is that we did not use a technique of rectification and averaging. The ipsilateral MEPs in adult patients with acquired disease are usually small, their latency being longer than the contralateral MEPs. Averaging of rectified EMG traces might be preferable for detecting such responses. The second reason might be that we used a focal coil and stimulated only the primary motor cortex. The origin of the ipsilateral MEPs is not yet well established but the premotor cortex (more frontal than the primary motor cortex) and the corticoreticulospinal tract are candidates (Caramia *et al*., 2000). The third possible reason is the difference in the investigation periods. The patients with poor recovery reported by Netz *et al*. (1997) were examined in more chronic stages after onset, whereas most of the present patients were in an early stage. Even if the

ipsilateral motor responses are a purposeful plastic phenomenon, they might play only a non-significant role in motor recovery, as the responsible corticofugal projection, such as the corticoreticulospinal tract, only forms a minor neuronal population compared with the pyramidal tract system. Judging from the present findings, the disruption of the TCI after unilateral cortical damage might produce only minor or non-significant effects on this system.

The clinical functional correlates of the ipsilateral motor cortical disinhibition need to be elucidated. Although there was no clumsiness or ataxia in the unaffected hands in our patients, our findings might be connected with the impairment of the dexterity of the intact hands that has been reported in hemiparetic stroke patients (Jones *et al*., 1989; Sunderland *et al*., 1999, 2000). These ipsilateral hand impairments are common within 1 month of stroke and gradually improve thereafter; the major causative factors appear to be cognitive deficits affecting perception and action control as well as ipsilateral sensorimotor involvement. The ipsilateral motor cortical disinhibition shown in the present study may have been one of the causes of the impaired ipsilateral hand dexterity; if so, there may be a difference in ipsilateral hand function between patients with stroke rostral and caudal to the corpus callosum. In addition, we wish to emphasize that the early motor cortex disinhibition caused by the disruption of TCI might recover in the chronic stage of stroke in spite of the persistence of the TCI disruption. This is also considered to be a late central reorganization. During this neuroplastic change, the above impairment in the dexterity of the ipsilateral hand might be gradually improved.

In conclusion, the present study provides further evidence of ipsilateral motor cortex disinhibition in the early stage of unilateral cortical stroke, which is distinct from findings in subcortical stroke caudal to the corpus callosum. The disruption of the TCI may be the main cause of the ipsilateral disinhibition, but this central functional alteration in the unaffected motor cortex would be likely to be normalized during the course of disease despite the lack of motor recovery, at least in a distinct subset of the patient population. Further investigations are needed to elucidate the precise functional significance of the early disinhibition of the unaffected motor cortex.

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