# Absence of Response to Early Transcranial Magnetic Stimulation in Ischemic Stroke Patients

## Prognostic Value for Hand Motor Recovery

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***Background and Purpose***—Transcranial magnetic stimulation (TMS) has been proposed as a prognostic tool in stroke patients. Most of the previous studies agree in considering the presence of motor-evoked potentials (MEPs) in the first days after a stroke as an indicator of good outcome. In the present study, we have assessed the prognostic value of the absence of response to early TMS on hand motor recovery in stroke patients with complete hand palsy at onset due to ischemia in the area of the middle cerebral artery.

***Methods***—Fifteen patients submitted to TMS within 48 hours of stroke onset (defined as day 1) and again after 1 year. They were also evaluated clinically on day 1 by a scale derived from the Medical Research Council (MRC) and by the National Institutes of Health (NIH) stroke scale; they were reevaluated by the same scales and by Barthel Index on day 365.

***Results***—On day 1, all the patients had complete hand palsy and no response to TMS; their NIH scores showed great variability. After 1 year, 6 of 15 patients regained small and prolonged MEPs, together with a very poor and not functionally useful motor recovery. NIH scores were significantly improved. Barthel Index scores showed large interindividual differences and were not correlated with MRC scores.

***Conclusions***—We conclude that in patients with complete hand palsy, the absence of response to TMS in the first hours is predictive of absent or very poor, not useful, hand motor recovery. **(*Stroke*. 1999;30:2666-2670.)**

**Key Words:** outcome ■ prognosis ■ stimulation, transcranial magnetic ■ stroke, ischemic



The quality of motor recovery after stroke is difficult to predict on the basis of only clinical data. Among other paraclinical methods, transcranial magnetic stimulation (TMS) has been proposed to predict motor outcome after a stroke,[1–4] but the results remain inconsistent,[5–7] probably because of the great variability of patients included and differences in the methodologies used. However, most authors[1–4] agree that persistent responses to TMS in the acute phase is an indicator of a good outcome. A previous study[8] has provided evidence of the usefulness of early TMS in the prediction of motor recovery in a homogeneous group of first-ever stroke patients with complete hand palsy due to ischemia in the area of the middle cerebral artery (MCA). After 2 weeks, all patients with initially preserved motor-evoked potentials (MEPs, >5% maximum motor response [$M_{max}$]) showed significant hand motor recovery. The long-term prognostic value of the absence of response to TMS was not specifically evaluated: after 2 weeks, all patients with no response showed no motor recovery, but it was not possible to extend the follow-up period. Of course, it is worthwhile to have early indicators of significant motor recovery, especially for the patient's motivation. Furthermore, obtaining early and reliable indications of the final degree of motor function recovery would also be useful for optimizing rehabilitation strategies and evaluating their costs.

The aim of the present study was to assess whether the absence of motor response to early performed TMS has a predictive value of hand motor function recovery after 1 year. The study was performed on stroke patients with complete hand palsy at the onset. All patients had an ischemic lesion in MCA territory.

## Subjects and Methods

### Patients

The study was approved by the local Ethics Committee and informed consent was obtained from patients or a close relative.

Fifteen first-ever stroke patients without response to TMS on the affected side were studied (mean age 60.7 years, range 39 to 76 years; 10 men and 5 women). All were hospitalized in the first hours after the onset of the stroke. They were treated according to current recommendations for the management of ischemic stroke[9] and

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received appropriate neurorehabilitation for the entire year. Patients included in the protocol fulfilled the following criteria: (1) first stroke due to MCA infarct; (2) complete hand palsy at onset; (3) confirmation of a stroke by CT scan, which showed an infarct in the MCA territory that was due to either thrombosis or embolism; (4) hospitalization within 48 hours of the onset of symptoms (defined as day 1); (5) absence of response to TMS on the affected side at day 1; and (6) presence of normal MEP on the healthy side. They were excluded if CT scan demonstrated primary cerebral hemorrhage or a lacunar infarct or if the patient was comatose, in terminal phase, or unable to understand simple orders.

## Methods

Patients were examined clinically and underwent TMS within the 48 hours after the onset of the symptoms (defined as day 1) and again at day 365, as outpatients. The location of the infarct was determined by a CT scan performed at least 1 week after stroke onset.

### *Magnetic Stimulation*

Patients lay supine in a quiet room. Magnetic stimulation was performed by use of a Magstim Novametrix 200 magnetic stimulator with a 9-cm mean diameter circular coil (Novametrix Inc). Cortical stimulation was performed with the coil held tangentially over the vertex; stimulation intensity was set at 100% of maximum stimulator output. Both hemispheres were stimulated. The left hemisphere was stimulated by a counterclockwise current; the right hemisphere, by a clockwise current. The affected side was always stimulated before the healthy one. When the muscle remained inexcitable with the coil in the "standard" position, it was moved slightly around to ensure that no responses could be elicited. Cervical motor roots were stimulated by the same coil applied over the seventh cervical spinal level with stimulation intensity at 100%. A counterclockwise current was used to stimulate the right arm cervical roots, and a clockwise current was used for the left ones. MEPs were recorded by surface electrodes fixed over the first dorsal interosseus muscle and amplified with a Medelec Premier amplifier (Oxford Instruments) with gains of 20 $\mu$V and 1 mV/division (band-pass 30 Hz to 3 kHz). Subjects were studied while producing a weak contraction of the recorded muscle, or of contralateral homologous muscle[10] if no voluntary contraction could be achieved, which was always the case on the affected side at day 1. A 100-millisecond poststimulus period was analyzed. Peak-to-peak amplitudes were measured, and 4 consecutive responses were averaged. Latencies were measured between the stimulation artifact and the onset of the first negative departure from the baseline, excluding random electromyographic activity when MEPs were recorded during voluntary contraction. A MEP was considered absent if no response could be obtained with 4 stimulations at 100% intensity. Four responses after cervical stimulation were recorded from the first dorsal interosseus muscle at rest. The longest MEP latency after cervical stimulation was taken as peripheral latency. Total motor conduction time (TMCT) was the shortest latency between cortical stimulation and muscle response.[10] Central motor conduction time (CMCT) was evaluated by subtracting peripheral latency from TMCT. $M_{max}$ after electrical stimulation of the ulnar nerve was also elicited, and the amplitude of MEPs after cortical stimulation was expressed as the MEP/$M_{max}$ ratio. MEP amplitude and CMCT were also measured on the healthy side at day 1. CMCT and the amplitude of MEPs were compared with the normative data of our laboratory.[11] CMCT was considered prolonged at >8.2 milliseconds (mean+2.5 SD of the mean) under voluntary contraction or >10.3 milliseconds at rest, and amplitude was considered reduced at <20% $M_{max}$ (mean−2.5 SD of the mean) during voluntary contraction and <10% $M_{max}$ at rest.

### *Clinical Evaluation*

Hand muscle strength was assessed on days 1 and 365 by use of a rating scale derived from the Medical Research Council (MRC)[12]: 0 indicates no movement; 1, movement only if gravity is removed; 2, weakness against gravity; 3, weakness against slight resistance; 4, weakness against stronger resistance; and 5, normal strength. Each patient was also assessed by the National Institutes of Health (NIH) stroke scale[13] at days 1 and 365 and by the Barthel Index[14] at day 365.

The Wilcoxon matched pair test was used to assess the changes in NIH stroke scale between day 1 and day 365. Correlations between the clinical scales were calculated by the Spearman rank correlation test. At day 365, the differences in NIH and Barthel Index scores between the group without motor recovery and the small group with some motor improvement were evaluated statistically by the Mann-Whitney rank sum test.

## Results

The clinical and electrophysiological data of the 15 patients are shown in the Table. All 15 patients included had normal MEPs on the healthy side after stimulation of the contralateral cortex. After cervical stimulation, MEPs were elicited in all patients on both sides.

On day 1, all patients exhibited complete hand palsy (MRC score 0) and absence of response to TMS on the affected side after contralateral cortex stimulation. The median NIH score on day 1 was 13, with a great individual variability (scores from 9 to 20). CT scans showed a cortical-subcortical or subcortical infarct in the MCA territory, with large interindividual size differences. The infarct was in the right hemisphere in 6 subjects and in the left hemisphere in 9. Seven subjects presented a subcortical infarct, and 8 had a cortical-subcortical infarct.

No patient had a new ischemic stroke during the first year of follow-up.

On day 365, 6 of 15 patients had regained MEPs on the affected side, but with reduced amplitude and prolonged CMCT. All patients who presented responses to TMS on the affected side also showed some hand motor recovery, which was, however, very poor and not functionally useful (see Table). The MRC score was 1 in 2 patients and 2 in 4 patients; the mean MRC score of the whole group of 15 patients was 0.7. There was no significant correlation between NIH scores on day 1 and MRC scores on day 365 (by Spearman rank correlation). The 6 patients with some motor recovery exhibited largely variable NIH scores (9 to 20) on day 1. The median NIH score of the 15 patients on day 365 was 8, with great variability in individual values (scores from 3 to 13); compared with scores on day 1, they were nevertheless significantly improved ($P<0.001$, by Wilcoxon test). The median Barthel Index on day 365 was 45, with large interindividual differences (scores of 15 to 80). There was no significant correlation between Barthel Index scores and MRC scores on day 365 (by Spearman rank correlation). No significant correlation was found between Barthel Index scores and NIH scores on day 1.

On day 365, the median NIH score of the 6 patients with some motor recovery was 5.5; the median NIH score of the remaining 9 patients without motor improvement was 10. The difference was significant ($P<0.001$, by Mann-Whitney test). In the group of 6 patients with some hand motor improvement, the median Barthel Index score was 57.5, whereas it was 35 in the group of 9 patients without motor recovery; the difference was not significant (by Mann-Whitney test). On day 365, no subject with present MEP on the affected side had an MRC score of 0. The 6 patients who recovered some

**Clinical and Electrophysiological Data of the 15 Patients**

| Patient No. | Age, y | Sex | Infarct Side | Location | Barthel Index | NIH Scale Score | | MRC | | MEP Amplitude, % $M_{max}$ | | CMCT, ms | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day 365 | Day 1 | Day 365 | Day 1 | Day 365 | Day 1 | Day 365 | Day 1 | Day 365 |
| 1 | 58 | M | R | S | 35 | 14 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 70 | M | R | C/S | 35 | 15 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 42 | M | L | C/S | 70 | 16 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 48 | M | L | C/S | 60 | 12 | 7 | 0 | 1 | 0 | 2 | 0 | 12.8 |
| 5 | 55 | M | L | C/S | 50 | 15 | 12 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 53 | F | L | S | 70 | 9 | 3 | 0 | 2 | 0 | 2.1 | 0 | 18.9 |
| 7 | 61 | M | R | C/S | 55 | 9 | 6 | 0 | 1 | 0 | 1.8 | 0 | 13.5 |
| 8 | 39 | M | R | S | 70 | 9 | 5 | 0 | 2 | 0 | 6.6 | 0 | 19 |
| 9 | 74 | F | L | S | 15 | 13 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 76 | F | R | S | 45 | 17 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | 64 | M | L | S | 30 | 9 | 5 | 0 | 2 | 0 | 8.5 | 0 | 20.3 |
| 12 | 71 | M | L | C/S | 20 | 12 | 12 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 | 70 | F | R | S | 25 | 10 | 9 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | 67 | M | L | C/S | 40 | 20 | 8 | 0 | 2 | 0 | 13.0 | 0 | 10.4 |
| 15 | 62 | F | L | C/S | 80 | 17 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |

CS indicates cortical-subcortical; S, subcortical; R, right; and L, left. Control values for amplitude are 10 to 70 (mean±2.5 SD); control values for CMCT are 5.1 to 10.3 (mean±2.5 SD). MRC scale ranges from 0 (indicating no movement) to 5 (indicating normal strength).

hand muscle strength had cortical-subcortical (n= 3) or subcortical (n=3) infarcts, with large variability in size.

## Discussion

The technique of TMS is easy to perform, rapid, inexpensive, safe, and painless.[15] It provides objective and reliable data. Several previous studies have indicated that TMS may usefully predict the outcome of a stroke[1–4] and have suggested that the persistence of response to TMS in the acute phase is an indicator of satisfactory recovery. However, the prognostic value of the absence of MEPs in the first days after a stroke remains uncertain. Chu and Wu[1] observed that when response to TMS was absent, the outcome was variable. Heald et al[2] concluded that the patients with absent responses had a high risk of poor functional recovery after 1 year, even if some patients reached a functionally useful manual dexterity. In the study of Catano et al,[3] the patients who had no response generally recovered poorly, but there were exceptions. More recently, similar observations have been made by Escudero et al.[4] However, in all these studies, the group with absent MEPs included patients with a variable degree of motor deficit. This fact could largely contribute to the variability of the reported results. In a previous work,[8] which included only patients with complete hand palsy, the absence of response to TMS during the first 24 hours was not followed by motor recovery after 2 weeks; a later evaluation was not possible because many patients did not come back as outpatients.

In the present study, we have assessed, with a 1-year follow-up period, the prognostic value of the absence of response to early TMS in a homogeneous group of first-stroke patients with complete hand palsy at onset due to an



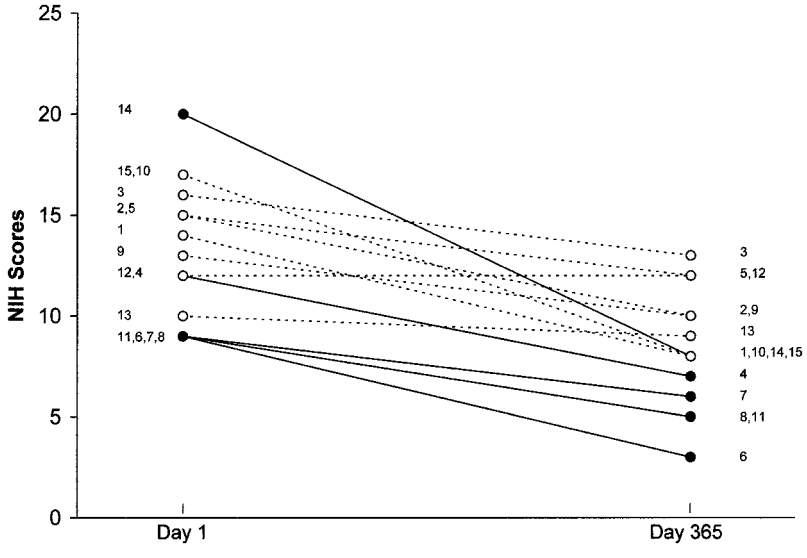


**Figure 1.** Evolution of individual NIH scores between day 1 and day 365. Patients 1 to 15 (see Table) are indicated beside the symbols. Dotted lines indicate the patients without hand motor recovery; solid lines indicate patients with some hand motor improvement.

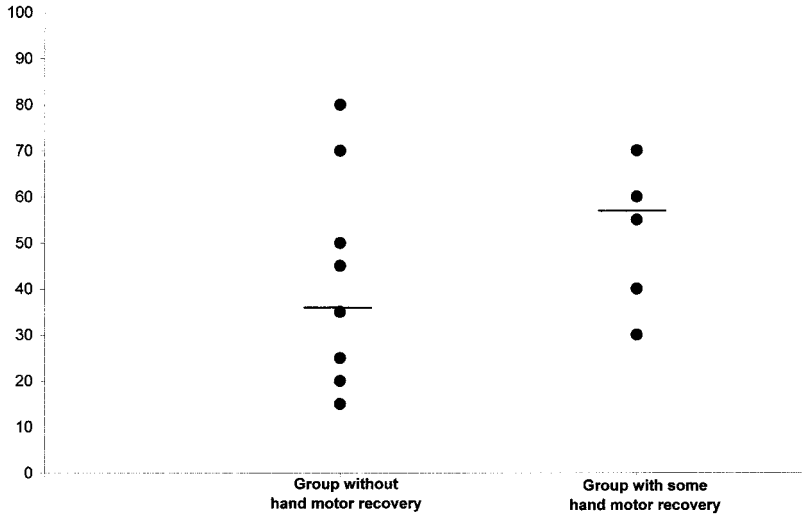


**Figure 2.** Individual Barthel Index scores on day 365 are shown for the group of patients without hand motor recovery and for the patients with some hand motor improvement. Although the Barthel Index score distribution is larger and the median (indicated by the solid line) is lower for the group without hand motor recovery than for the group with some hand motor recovery, the differences are not significant.

infarct in the MCA territory. In fact, it has been reported that most of the motor recovery after a stroke occurs within the first month[16,17] but that improvement can continue for up to 6 months[18] and sometimes for up to 1 year.[19] For that reason, a 1-year follow-up period seems reasonable. The limited number of patients in the present study is due to strict inclusion criteria and, in the case of disabled patients, the difficulty of returning to the hospital for reassessment. For this reason, control studies at intermediate times (3 to 6 months) have not been performed.

In the present study, on day 365, a strict parallelism was seen between the reappearance of muscle strength and the reappearance of responses to TMS. Heald et al[20] have reported that the majority of patients regain MEP within 3 months. Because we did not study the patients after such a delay, we were not able to confirm these observations. In the same study, the number of patients who regained MEPs was higher (12 of 16) than in the present group, and in some patients (n=5), responses had normal CMCT. These discrepancies could be explained by the fact that the group was formed by patients with different degrees of hand motor deficit, whereas the present study included only patients with complete hand palsy. In our patients, the degree of hand motor recovery achieved after 365 days was very poor and not functional; in fact, the highest MRC score,[2] which was reached by patients 6, 8, 11, and 14, was not sufficient for the functional use of the hand. It is clear that the ability to perform some movement against gravity (MRC score of 2) is not enough to use the hand even for the most simple activity of daily living, eg, using a spoon. The absence of a good correlation between the Barthel Index and MRC scores on day 365 is consistent with this finding.

Moreover, the great variability of Barthel scores on day 365 suggests that TMS is useful in indicating some degree of motor recovery; however, it is not able to predict the global functional improvement when useful hand motor recovery does not occur. On the other hand, functional recovery, expressed by the Barthel Index, also depends on factors other than hand muscular strength. Similar considerations have been recently expressed by Escudero et al.[4]

The global neurological condition of the 15 patients, indicated by NIH scores, showed a significant improvement between days 1 and 365 and presented large interpatient variability both on day 1 and on day 365. These results suggest that the final degree of hand motor recovery seems to be independent of the initial general neurological conditions and their improvement. On day 365, the differences observed in NIH scores between the group of 6 patients with a little hand motor recovery and the group of patients with no hand motor improvement can be explained, in large part, by the characteristics of the items included in the NIH scale. In fact, some items are specifically indicated for the acute phase of the stroke, but they lose of significance after 1 year. Thus, the number of items that influence the global NIH score is restricted, and an improvement in hand muscle strength inevitably brings significantly lower NIH scores (Figure 1). On the other hand, the Barthel scores of the 2 groups of patients are not significantly different (Figure 2). These data indicate that the hand motor recovery observed in the first group of 6 patients influences the final global neurological conditions but that it is not sufficient to allow a better functional recovery.

In the present series, NIH scores on day 1 were not significantly correlated with MRC scores on day 365, and there were patients showing a clear improvement in NIH scores and total absence of hand motor recovery (refer to patient 10 in the Table). In the small group of patients with some motor recovery, NIH scores on day 1 were again largely variable (ranging from 9 to 20). There was no significant correlation between the Barthel Index scores and NIH scores on day 1; therefore, the NIH scale does not seem helpful in predicting the final outcome. The present data confirm what was observed in a previous work.[8]

In conclusion, our data suggest that in patients with complete hand palsy, TMS performed early is a useful tool in predicting final hand motor recovery. The absence of responses to TMS in the first 48 hours is predictive of absent or very poor and, in all cases, not functional hand motor recovery. This fact is independent of the general neurological conditions at the onset. If confirmed in a larger series of

patients, TMS could be a very useful tool in planning and optimizing rehabilitation strategies and adding new insight to clinical and neuroradiological data. This technique might be used to identify homogeneous groups of stroke patients on whom the effectiveness of new drugs and rehabilitation techniques could be tried.

## References


1. Chu N, Wu T. Motor response patterns and prognostic value of transcranial magnetic stimulation in stroke patients. In: Lissens M, ed. *Clinical Applications of Magnetic Transcranial Stimulation.* Leuven, Belgium: Peeters Press; 1992:127–145.
2. Heald A, Bates D, Cartlidge NEF, French JM, Miller S. Longitudinal study of central motor conduction time following stroke, II: central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. *Brain*. 1993;116:1371–1385.
3. Catano A, Houa M, Caroyer JM, Ducarne H, Noel P. Magnetic transcranial stimulation in non-haemorrhagic sylvian strokes: interest of facilitation for early functional prognosis. *Electroencephalogr Clin Neurophysiol*. 1995;97:349–354.
4. Escudero JV, Sancho J, Bautista D, Escudero M, López-Trigo J. Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. *Stroke*. 1998;29:1854–1859.
5. van Rijckevorsel-Harmant K, Boon V. Central magnetic stimulation, somatosensory potentials and clinical evaluation during a rehabilitation treatment in hemiplegic patients. *Electroencephalogr Clin Neurophysiol*. 1993;87:102. Abstract.
6. Zgur T, Prevec TS, Golfar N. Correlation of motor evoked potentials to motor deficit during the recovery of ischemic stroke. *Electroencephalogr Clin Neurophysiol*. 1993;87:102. Abstract.
7. Arac N, Sagduyu A, Binai S, Ertekin C. Prognostic value of transcranial magnetic stimulation in acute stroke. *Stroke*. 1994;25:2183–2186.
8. Rapisarda G, Bastings E, Maertens de Noordhout A, Pennisi G, Delwaide PJ. Can motor recovery in stroke patients be predicted by early transcranial magnetic stimulation? *Stroke*. 1996;27:2191–2196.
9. Marshall RS, Mohr JP. Current management of ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 1993;56:6–16.
10. Hess CW, Mills KR, Murray MNF. Responses in small hand muscles from magnetic stimulation of human brain. *J Physiol (Lond)*. 1987;388:397–419.
11. Maertens de Noordhout A. *Stimulation Percutanée du Cortex Moteur Chez l'Homme: Données Physiologiques et Utilisation Clinique*. Liège, Belgium: Mardaga; 1991. Thesis.
12. Medical Research Council. *Aids to Examination of the Peripheral Nervous System.* London, England: HMSO; 1976.
13. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. *Arch Neurol*. 1989;56:660–662.
14. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability. *Int Disabil Stud*. 1988;19:604–607.
15. Barker AT, Freeston IL, Jalinous R, Jarratt JA. Magnetic and electric stimulation of the brain: safety aspects. In: *Noninvasive Stimulation of Brain and Spinal Cord.* New York, NY: Alan R Liss Inc; 1988: 131–144. Rossini PM, Marsden CD, eds. *Neurology and Neurobiology,* vol 41.
16. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke: outcome assessment and sample size requirements. *Stroke*. 1992;23:1084–1089.
17. Duncan PW, Goldstein LB, Horner RD, Landsman PB, Samsa GP, Matchar DB. Similar motor recovery of upper and lower extremities after stroke. *Stroke*. 1994;25:1181–1188.
18. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19:1497–1500.
19. Wade DT, Hewer RL. Motor loss and swallowing difficulty after stroke: frequency, recovery, and prognosis. *Acta Neurol Scand*. 1987;76:50–54.
20. Heald A, Bates D, Cartlidge NEF, French JM, Miller S. Longitudinal study of central motor conduction time following stroke, I: natural history of central motor conduction. *Brain*. 1993;116:1355–1370.