

Conduction deficits of callosal fibres in early multiple sclerosis

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Abstract

Objective—To study the diagnostic usefulness of transcallosal inhibition (TI) elicited by transcranial magnetic stimulation (TMS) in detecting central conduction deficits in early multiple sclerosis. **Corticospinally mediated excitatory responses evoked by TMS are accepted as a sensitive diagnostic tool in multiple sclerosis. Recently, TI evoked by TMS has been introduced as a new paradigm to test the function of callosal fibres interconnecting both hand associated motor cortices.**

Methods—Focal TMS of the motor cortex was performed in 50 patients with early relapsing-remitting multiple sclerosis. **Corticospinally mediated (central motor latencies, amplitudes) and transcallosally mediated (onset latency and duration of TI) stimulation effects were investigated.**

Results—TMS disclosed abnormalities of corticospinally mediated responses in 62% and of TI in 80% of the patients.

Conclusion—The assessment of TI allows the discovery of lesions within the periventricular white matter that were not accessible by neurophysiological techniques before. **This new paradigm increases the sensitivity of TMS with which to detect central conduction deficits in early multiple sclerosis.**

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Focal transcranial magnetic stimulation (TMS) of the hand associated motor cortex leads to a contralateral excitatory motor response mediated via fast conducting monosynaptic corticospinal fibres^{1–3} followed by a postexcitatory silent period⁴ and to an inhibition of the homotopic contralateral primary motor cortex. This transcallosal inhibition (TI) can be visualised by the suppression of tonic voluntary EMG activity originating from the contralateral motor cortex and is mediated by slowly conducting fibres^{5,6} passing through the posterior trunk of the corpus callosum.⁷ TI was found to be altered in patients with brain trauma and hydrocephalus and might therefore be a useful diagnostic tool with which to investigate the conduction deficits in a fraction of callosal fibres.^{6–8} Previous investigations of patients with multiple sclerosis using TMS have focused on corticospinally mediated responses. Various studies showed prolonged central motor conduction times, reduced amplitudes, and polyphasic potentials as corre-

lates of demyelination and axonal loss.^{9–14} As the heaviest concentration of white matter lesions is often seen in paraventricular locations and the corpus callosum, changes of callosal fibre function and an impairment of TI should also be expected in multiple sclerosis.^{15,16} Only one previous study demonstrated abnormalities of TI in patients with multiple sclerosis.¹⁷

In this study we investigated patients in an early stage of multiple sclerosis to address the following questions:

- (1) How frequent are TI abnormalities?
- (2) Which indices of TI are changed (onset latency and duration of TI; transcallosal conduction time)?
- (3) Does the investigation of TI increase the sensitivity of TMS in detecting central conduction deficits in multiple sclerosis? Preliminary results have been reported in abstract form.¹⁸

Methods

PATIENTS

Fifty patients (18 men and 32 women) aged 16 to 52 years (mean 33 years) with relapsing-remitting multiple sclerosis were investigated with ethics committee approval. Based on the criteria by Poser *et al*¹⁹ 43 patients had laboratory supported definite multiple sclerosis, seven patients were classified as having clinically definite multiple sclerosis. The duration of disease lay between 0.5 and 6 years (mean 2.4 years) and the expanded disability status scale (EDSS)²⁰ score between 0 and 3.5 (mean 2.0). Twenty five healthy volunteers (11 men and 14 women) aged 23 to 46 years (mean 31.8 years) served as a control group and were subjected to the same experimental procedures as the patients. Written informed consent was obtained from all subjects investigated.

MAGNETIC STIMULATION AND RECORDING

Focal TMS of the motor cortex was performed with a figure of eight coil (outside diameter of half coil, 8.5 cm) of the Magstim 200 stimulator (2 Tesla version; Magstim Company, Dyfed, UK) to elicit corticospinally mediated contralateral EMG responses in the first dorsal interosseous muscle (FDI) and TI of tonic voluntary EMG activity in the FDI ipsilateral to stimulation. TMS was performed during maximal tonic muscle contraction over the individually determined point from which maximal EMG responses could be obtained. This point lay, on average, 6 cm lateral to the vertex and 1 cm anterior to the interaural line. In the axis of the stimulation coil, the currents were directed anteroposteriorly (induced currents with opposite orientation) because this direction

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is the most effective for eliciting TI.²¹ To prevent fatigue the patients were asked to relax their hand muscles for about 2–3 seconds after each stimulus. Cortical stimulation was performed with 80% of the maximum stimulator output. For such a stimulus intensity, TI could always be elicited in normal subjects, and the onset latency and duration of TI did not change further with increasing stimulus intensities.⁶ Twenty consecutive EMG traces were recorded.

Corticospinally mediated responses in the tibialis anterior muscle (TA) were elicited using a circular electromagnetic coil (outside diameter, 11.6 cm) centred over the vertex.

Counterclockwise and clockwise currents were used for eliciting responses in the right and left TA respectively.²² Cortex stimulation was performed with 1.2 times the response threshold of slightly contracted muscles. Ten consecutive EMG responses of tonically contracted TAs (50% of maximum force) were recorded.

Peripheral latencies were obtained by magnetic stimulation of cervical and lumbar spinal roots using the circular coil. EMG activity of hand and leg muscles was recorded bilaterally with surface electrodes (area 19 mm²). The EMG signals were amplified and filtered with a special device.²³ Data were collected with a

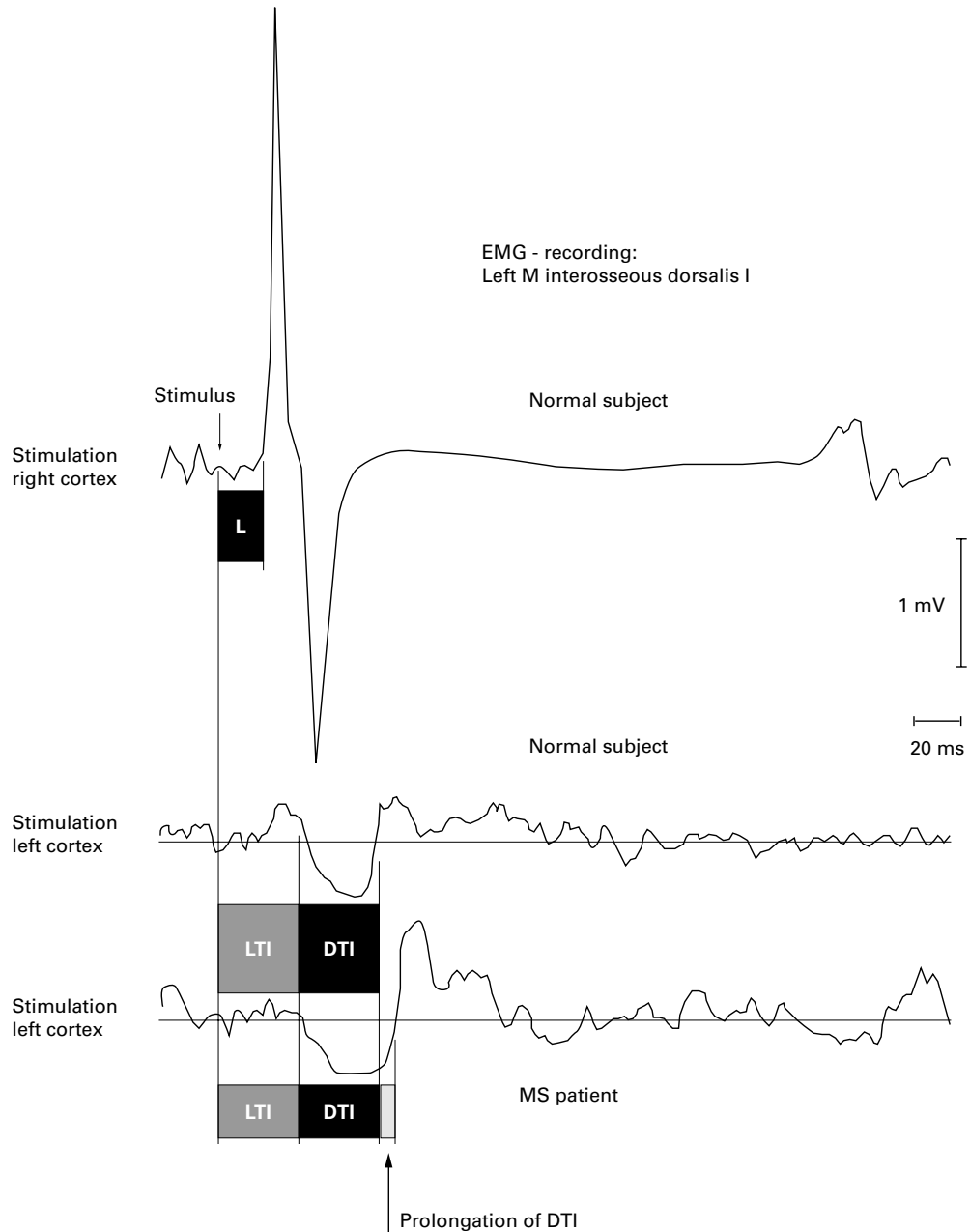


Figure 1 Excitatory and inhibitory EMG responses in the FDI after focal TMS of the hand associated motor cortex contralateral (top trace) and ipsilateral (lower two traces) to stimulation. The onset latency (LTI) and duration (DTI) of transcallosal inhibition are compared for a normal subject (middle trace) and one exemplary patient with multiple sclerosis (MS) (third trace). The duration of TI in the patient with multiple sclerosis is prolonged. Stimulation was performed with 80% of the maximum stimulator output during bilateral maximal tonic hand muscle contraction. L=onset latency of contralateral excitatory response.

Table 1 Corticospinally mediated excitatory (hand and leg muscles) and callosally mediated inhibitory (hand muscles) motor effects in 50 MS patients and in 25 normal subjects

Muscle	Parameter	Normal subjects 50 hands and 50 legs			MS patients 100 hands and 100 legs		Abnormal responses (muscles/patients)
		Mean (SD)	Range	Limits of normal range	Mean (SD)	Range	
FDI	Central motor latency (ms)	6.7 (1.0)	4.6–9.2	<9.2 (<mean+2.5 SD)	7.3 (1.6)	4.8–12.0*	10/7
	Amplitude (mV)	7.6 (1.4)	4.0–10.6	>4.0 (>lowest value)	5.7 (2.3)	0.8–10.0**	24/17
	Latency of TI (ms)	35.7 (3.2)	29.8–43.0	<43.9 (<mean+2.5 SD)	36.9 (4.5)	27.4–50.4	10/9
	Duration of TI (ms)	24.9 (3.0)	19.6–32.2	<32.6 (<mean+2.5 SD)	34.8 (10.9)	10.0–69.8**	51/36
	Transcallosal conduction time (ms)	15.3 (2.7)	9.0–20.8	<22.2 (<mean+2.5 SD)	15.6 (3.6)	7.0–24.4	2/2
TA	Central motor latency (ms)	14.2 (2.1)	10.0–19.0	<19.4 (<mean+2.5 SD)	19.0 (5.3)	11.2–33.4**	40/24
	Amplitude (mV)	4.2 (2.2)	1.0–11.6	>1.0 (>lowest value)	3.2 (2.1)	0.3–8.3**	3/3

*p<0.05; **p<0.01. FDI=first dorsal interosseous muscle; TA=tibialis anterior muscle; TI=transcallosal inhibition.

personal computer using a CED 1401 interface (CED, Cambridge, UK) and a data collection program (SIGAVG; sampling frequency of 5000/s per channel).

RESPONSE INDICES

In hand muscles contralateral to stimulation the response thresholds, amplitudes and central motor latencies (CMLs) of corticospinally mediated responses were determined. The response thresholds (percentage of maximum stimulator output) were determined for the relaxed hands and were defined as the stimulus intensity at which responses of more than 0.2 mV occurred in about half of the trials. The amplitudes of the cortically evoked contralateral EMG responses were determined peak to peak for 20 averaged consecutive hand responses. The CMLs were calculated for rectified and averaged EMG signals by subtracting the longest peripheral conduction time after magnetic root stimulation from the onset latency of the cortically elicited contralateral EMG response.

Onset latency and duration of TI were determined for rectified and averaged EMG activity of the FDI ipsilateral to cortex stimulation. The onset latency of TI was measured from the stimulus to a point where the signal of the averaged tonic EMG activity clearly fell under the mean amplitude of the EMG activity before the stimulus. The duration of TI was measured from its onset to a point where the EMG activity reached the mean amplitude of the baseline EMG activity before the stimulus. Transcallosal conduction times were determined by subtracting the onset latency of the corticospinally mediated EMG response from the onset latency of TI in the same FDI. Figure 1 shows how the different indices of corticospinally and callosally mediated motor effects were determined and shows the typical findings of a normal subject and one patient with multiple sclerosis. In leg muscles, CMLs and amplitudes of corticospinally mediated responses were determined in the same way as described for the hand muscles but only for 10 consecutive responses.

Mean values and SDs were calculated for each index. As the upper limit of normality, the mean value +2.5 SDs of the control group was accepted for the CML, latency, and duration of TI, and the transcallosal conduction time. Amplitudes were defined as reduced when they were smaller than the smallest amplitude of the control group.

VISUAL EVOKED POTENTIALS

Visual evoked potentials (VEPs) were obtained from 46 of the patients using a chequer board pattern reversal device. VEP latencies were determined to the first major positive peak.²⁴ The upper limit of the VEP latency was 114 ms (mean value of normal subjects+2.5 SD), side to side differences >8 ms were regarded as pathological.

MAGNETIC RESONANCE IMAGING STUDY

In 32 patients sagittal and axial T2 weighted MRI of the cerebrum were evaluated. Site and size of hyperintense lesions within the course of callosal fibres were assessed. The location of the lesions was attributed to the anterior, middle, or posterior third of the corpus callosum and its fibre radiation. Within each of the three regions, the percentage of the extension of the lesions was rated as 0 (no lesion), 1 (<50%), or 2 (≥50%). We developed an individual “MRI lesion score” by adding the scores of the three callosal regions. Thus the MRI lesion score lay between 0 and 6.

STATISTICAL ANALYSIS

Spearman's rank correlation was used to analyse relations between variables and the Mann-Whitney *U* test was applied for group data comparisons.

Results

TRANSCRANIAL MAGNETIC STIMULATION

In 25 normal subjects and 50 patients with multiple sclerosis, motor responses evoked by TMS of the motor cortex were recorded

Table 2 Percentage of MS patients (n=50) with abnormal corticospinally mediated excitatory responses (hand and leg muscles) and callosally mediated inhibition (hand muscles). Stimulation effects were defined as abnormal when at least one parameter of corticospinally mediated responses (central motor latency, amplitude) or of transcallosal inhibition (latency and/or duration) lay outside the normal range

	FDI	TA
Contralateral excitatory response:		
Unilateral	22	16*
Bilateral	18	32
Unilateral or bilateral	40	48
Hand and/or leg muscle	62	
Transcallosal inhibition:		
Unidirectional	42	—
Bidirectional	38	—
Unidirectional or bidirectional	80	—
At least one abnormality in hand muscles	88	
At least one abnormality in hand and/or leg muscles	34	

*No response in one patient. FDI=first dorsal interosseous; TA=tibialis anterior.

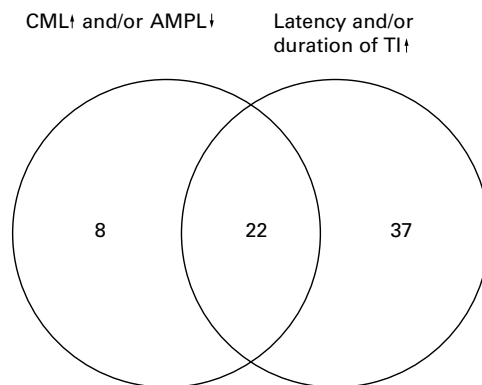


Figure 2 Summary of individual patterns of abnormalities of contralateral corticospinally mediated responses (left circle; CML central motor latency, AMPL amplitude) and of transcallosal inhibition (TI; right circle; latency, duration). Stimulation effects in 100 hand muscles of 50 patients with multiple sclerosis. In 33 hands no abnormalities were detected.

bilaterally from the FDI and TA. Corticospinally mediated excitatory responses and TI occurred in all healthy subjects. In the group of patients with multiple sclerosis, corticospinally mediated responses were absent in one leg muscle; in two patients, TI was unilaterally absent. Table 1 summarises the normal data, the limits of the normal range, and the results of the experiments.

The thresholds of hand motor responses did not differ between patients with multiple sclerosis and normal subjects (39.5 (8.0%) *v* 41.6 (7.2%), $p=0.25$). In patients with multiple sclerosis, the CMLs were significantly longer and the amplitudes of hand and leg motor responses were smaller compared with the control group. Whereas the latency of TI and the transcallosal conduction time were the same in patients and normal subjects, the duration of TI was significantly prolonged in the patients (table 1).

Corticospinal conduction deficits were indicated by prolonged CMLs to 10% of the recorded hand muscles and 40% of the leg muscles, and by reduced amplitudes in 24% of the hand and 3% of the leg muscles. An increased duration of TI was found in 51%, a

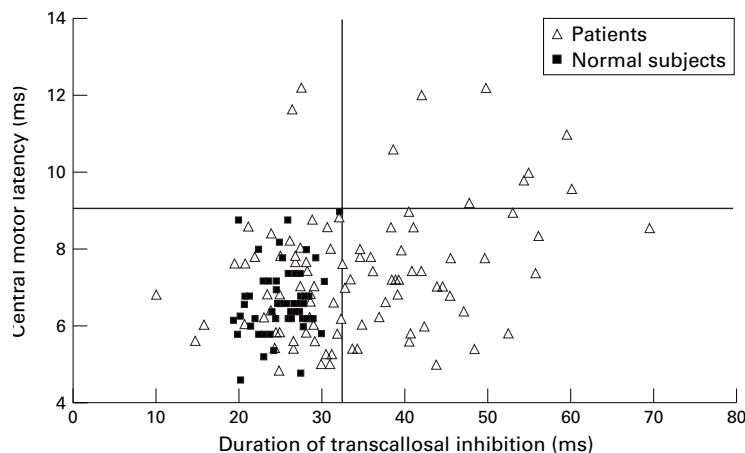


Figure 3 Central motor latencies of corticospinally mediated hand motor responses plotted against the duration of transcallosal inhibition of tonic EMG activity in the same muscles. Results of 50 hand muscles of 25 healthy subjects and 100 hand muscles of 50 patients with multiple sclerosis. Values above the horizontal and right of the vertical line are pathological. Stimulation and recording conditions as described in fig 1.

prolonged latency of TI in 10%, a prolonged transcallosal conduction time in 2%, and an absence of TI in 2% of the recorded hand muscles.

To describe the sensitivity of detecting functional deficits in the investigated corticospinal and callosal fibres, the percentage of abnormal excitatory and inhibitory motor responses is summarised in table 2. In 47 of 50 patients, at least one index of excitatory (FDI, TA) and/or inhibitory (FDI) motor responses was abnormal. When the change of at least one response index in one hand muscle was regarded as pathological, a conduction deficit of the corticospinal fibres could be detected in 40% and increased to 62% when leg motor responses were additionally considered. However, 80% of the patients had a unilateral and/or bilateral delay of the onset latency of TI and/or a prolongation of the duration of TI. Figure 2 shows the individual patterns of abnormal corticospinally mediated excitatory and transcallosally mediated inhibitory hand motor effects of TMS in the patients with multiple sclerosis. Isolated abnormalities of TI were four times more frequent than isolated deficits of corticospinal tract function.

Figure 3 shows the correlation between the CMLs of excitatory hand motor responses and the duration of the TI in the same muscle. The CML was prolonged in 10 hand muscles (seven patients), whereas the duration of TI was prolonged in 51 hand muscles (36 patients). Both indices were abnormal in eight hand muscles (six patients). In only one patient (two hand muscles) did an isolated prolongation of the CML occur.

VISUAL EVOKED POTENTIALS

Figure 4 shows the number of prolonged VEP latencies in comparison with corticospinal and callosal conduction deficits detected by TMS. VEP latencies were prolonged in 25 of 46 patients (in seven patients bilaterally). In only two patients was the central conduction deficit confined to the visual pathway, whereas 20 patients with normal VEPs had abnormal excitatory and/or inhibitory responses elicited by TMS.

MAGNETIC RESONANCE IMAGING STUDY

Eighteen patients had lesions in the anterior, 28 in the middle, and 22 in the posterior third of the corpus callosum and/or the respective adjacent pericallosal white matter. The lesion size did not differ between these anatomical regions. Two patients had no lesion—that is, an MRI lesion score of zero. The scores of the remaining patients amounted to: 1 in four patients, 2 in 12 patients, 3 in six patients, 4 in one patient, 5 in four patients, and 6 in three patients.

No correlation was found between the findings obtained with TMS and the three locations of lesions within the corpus callosum or the adjacent pericallosal white matter. However, the MRI lesion score correlated significantly with a prolonged duration of TI ($r=0.364$; $p<0.01$). None of the other indices elicited by TMS correlated with the MRI

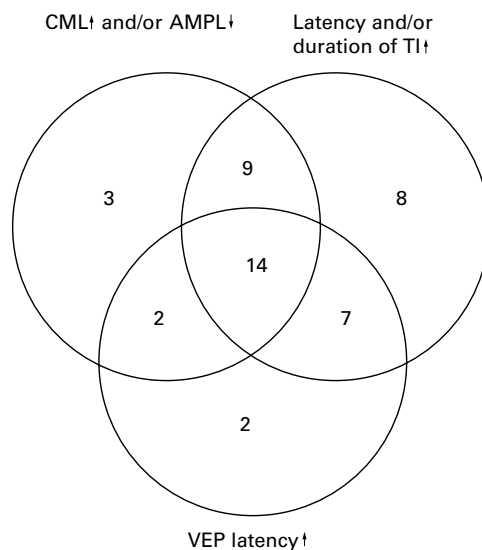


Figure 4 Summary of individual patterns of abnormalities of transcranially elicited contralateral excitatory responses (CML central motor latency, AMPL amplitude; upper left circle), of transcranially elicited transcallosal inhibition (TI; upper right circle; latency, duration) and of abnormal visual evoked potentials (VEPs; lower circle) in 46 patients with multiple sclerosis. In one patient no abnormalities were detected.

lesion score. One patient without any visible lesion on MRI had an isolated bidirectional prolongation of TI duration.

Discussion

The evaluation of the transient inhibition of tonic EMG activity in hand muscles ipsilateral to focal TMS represents a new approach with which to investigate interhemispheric connections of the hand associated motor cortices in humans.⁵⁻⁶ The evidence for a transcallosal pathway underlying TI came from the investigation of patients with agenesis or a transection of the corpus callosum.⁶⁻⁷ The fibres that mediate TI pass through the posterior trunk of the corpus callosum.⁷ The first diagnostic application was done in patients with vascular lesions located in the internal capsule where a residual function of the corticospinally de-efferented motor cortex was indicated by an intact TI.²⁵ In patients with hydrocephalus, a prolonged duration of TI was detected, which may reflect an increased dispersion of impulse propagation along stretched and compressed callosal fibres.⁸

In the present study, we assessed the function of callosal fibres in the early stages of multiple sclerosis with this new paradigm. The assessment of TI was found to be more sensitive than the evaluation of corticospinally mediated responses in detecting abnormalities of impulse conduction along central fibres. TI was abnormal in 80% of the patients, whereas the amplitudes and/or CMLs of corticospinally mediated responses were abnormal in only 62%. The most frequent abnormality was a prolonged duration of TI.

The second finding is by contrast with a recent study by Borojoerdi *et al*, who detected a prolonged transcallosal conduction time as the main abnormality in a group of 24 unselected

patients with multiple sclerosis.¹⁷ The low percentage of increased duration of TI might be explained by the wide range of this index in that study. Furthermore, the patients were heterogeneous for disease duration, motor deficits, and the course of the disease. An important finding, however, was that a prolonged transcallosal conduction time or an absence of TI correlated with disease duration: In eight patients with at least a unilaterally prolonged transcallosal conduction time, the mean disease duration was 6.4 (SD 3.7) years and, in the six patients with unilaterally absent TI, 9.3 (SD 7.1) years, both of which are significantly longer than in the group of nine patients with a mean disease duration of 2.9 (SD 3.1) years and normal transcallosal conduction times ($p=0.04$ for normal versus prolonged transcallosal conduction time; $p=0.03$ for normal versus absent TI; Mann-Whitney U test).¹⁷ Hence, a prolongation of transcallosal conduction times might be a characteristic feature of late disease stages.

In early multiple sclerosis, the increase in TI duration without a concomitant delay of the onset latency of TI could be due to demyelination of only a few callosal fibres. Impulse propagation along residual intact large diameter fibres would explain normal or only slightly delayed onset latencies of TI, whereas an impairment of the impulse propagation along fibres with smaller diameters would result in an increased dispersion of impulses arriving in the contralateral motor cortex, thus leading to a prolonged duration of TI. However, by contrast with the fast conducting and monosynaptic corticospinal system activated by TMS,²⁶ the characteristics of impulse propagation in the slowly conducting oligosynaptic or polysynaptic functional system mediating TI are unknown.⁶ Furthermore, changes in cortical excitability due to multiple sclerosis may contribute to the prolonged duration of TI, although until now this question has not been addressed.

In our study the frequency of corticospinal conduction deficits reached 62% when motor responses were recorded from hand and leg muscles. This confirms earlier reports that showed that the sensitivity can be increased when the lower limbs are included in the examination.¹²⁻¹³⁻²⁷ However, the assessment of TI in the present study on early multiple sclerosis was clearly found to be more sensitive in the detection of central conduction deficits than the evaluation of corticospinally mediated responses or of VEP latencies. This can be attributed to the heavy concentration of white matter lesions in paraventricular locations often involving the corpus callosum.¹⁵ This was also demonstrated by the positive correlation between a prolonged TI duration and the burden of periventricular lesions disclosed by MRI in our study. The finding of isolated abnormalities of TI allows the detection of dysfunctional callosal fibres that are not accessible by other neurophysiological techniques.

To confirm the diagnosis as early as possible is a prerequisite to provide patients with multiple sclerosis with potentially useful prophylactic

agents.²⁸ Apart from laboratory supported definite multiple sclerosis, where clinical or para-clinical evidence of only one CNS lesion is necessary, at least two lesions at different locations in the CNS must be demonstrated to establish the diagnosis.¹⁹ Hence, MRI as well as visual, auditory, sensory and magnetically evoked motor potentials are used to detect additional lesions.²⁹ In our study the assessment of TI was much more sensitive in detecting lesions in early multiple sclerosis than the well established investigation of corticospinal tract function by TMS and of visual evoked potentials.^{27 29 30} The combined investigation of TI and corticospinally mediated motor responses allowed us to detect central conduction deficits in 94% of the patients. Thus a more detailed TMS investigation including the assessment of TI can be recommended as a highly sensitive neurophysiological technique in patients suspected of having multiple sclerosis.

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- 1 Day BL, Rothwell JC, Thompson PD, et al. Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain* 1987;110:1191–1209.
- 2 Hess CW, Mills KR, Murray NM. Responses in small hand muscles from magnetic stimulation of the human brain. *J Physiol (Lond)* 1987;388:397–419.
- 3 von Giesen H, Roick H, Benecke R. Inhibitory actions of motor cortex following unilateral brain lesions as studied by magnetic brain stimulation. *Exp Brain Res* 1994;99:84–96.
- 4 Davey NJ, Romaiguere P, Maskill DW, et al. Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. *J Physiol (Lond)* 1994;477:223–35.
- 5 Ferbert A, Priori A, Rothwell JC, et al. Interhemispheric inhibition of the human motor cortex. *J Physiol (Lond)* 1992;453:525–46.
- 6 Meyer BU, Röricht S, Gräfin von Einsiedel H, et al. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 1995;118:429–40.
- 7 Meyer BU, Röricht S, Woiciechowsky C. Topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. *Ann Neurol* 1998;43:360–9.
- 8 Röricht S, Meyer BU, Woiciechowsky C, et al. Callosal and corticospinal tract function in patients with hydrocephalus: a morphometric and transcranial magnetic stimulation study. *J Neurol* 1998;245:280–8.
- 9 Hess CW, Mills KR, Murray NM. Measurement of central motor conduction in multiple sclerosis by magnetic brain stimulation. *Lancet* 1986;ii:355–8.
- 10 Hess CW, Mills KR, Murray NM, et al. Magnetic brain stimulation: central motor conduction studies in multiple sclerosis. *Ann Neurol* 1987;22:744–52.
- 11 Caramia MD, Bernardi G, Zarola F, et al. Neurophysiological evaluation of the central nervous impulse propagation in patients with sensorimotor disturbances. *Electroencephalogr Clin Neurophysiol* 1988;70:16–25.
- 12 Jones SM, Streletz LJ, Raab VE, et al. Lower extremity motor evoked potentials in multiple sclerosis. *Arch Neurol* 1991;48:944–8.
- 13 Ravnborg M, Liguori R, Christiansen P, et al. The diagnostic reliability of magnetically evoked motor potentials in multiple sclerosis. *Neurology* 1992;42:1296–301.
- 14 Kidd D, Thompson PD, Day BL, et al. Central motor conduction time in progressive multiple sclerosis. Correlations with MRI and disease activity. *Brain* 1998;121:1109–16.
- 15 Gean-Marton AD, Vezina LG, Marton KI, et al. Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis. *Radiology* 1991;180:215–21.
- 16 Raine C. The neuropathology of multiple sclerosis. In: Raine C, McFarland HM, Tourtellotte WW, eds. *Multiple sclerosis. Clinical and pathogenetic basis*. London: Chapman and Hall, 1997:151–71.
- 17 Boroojerdi B, Hungs M, Mull M, et al. Interhemispheric inhibition in patients with multiple sclerosis. *Electroencephalogr Clin Neurophysiol* 1998;109:230–7.
- 18 Schmierer K, Röricht S, Niehaus L, et al. Impaired transcallosal inhibition: an early indicator of central conduction deficits in multiple sclerosis [abstract]. *Electroencephalogr Clin Neurophysiol* 1998;109(suppl 1001):53.
- 19 Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227–31.
- 20 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.
- 21 Meyer BU, Kühn A, Röricht S. Influence of the direction of induced currents on callosally and corticospinally mediated electromyographic responses following magnetic motor cortex stimulation in man [abstract]. *J Physiol (Lond)* 1996;497:34–5.
- 22 Macdonell RA, Shapiro BE, Chiappa KH, et al. Hemispheric threshold differences for motor evoked potentials produced by magnetic coil stimulation. *Neurology* 1991;41:1441–4.
- 23 Jakob C, Mathis J, Weyh T, et al. Artifact reduction in magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 1993;89:287–9.
- 24 Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. *Lancet* 1972;i:982–5.
- 25 Boroojerdi B, Diefenbach K, Ferbert A. Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. *J Neurol Sci* 1996;144:160–70.
- 26 Amassian V, Cracco R. Human cerebral cortical responses to contralateral transcranial stimulation. *Neurosurgery* 1987;20:148–55.
- 27 Mayr N, Baumgartner C, Zeithofer J, et al. The sensitivity of transcranial cortical magnetic stimulation in detecting pyramidal tract lesions in clinically definite multiple sclerosis. *Neurology* 1991;41:566–9.
- 28 Hohlfeld R. Biotechnological agents for the immunotherapy of multiple sclerosis. Principles, problems and perspectives. *Brain* 1997;120:865–916.
- 29 Giesser BS, Kurtzberg D, Vaughan HG, et al. Trimodal evoked potentials compared with magnetic resonance imaging in the diagnosis of multiple sclerosis. *Arch Neurol* 1987;44:281–4.
- 30 Lee KH, Hashimoto SA, Hooge JP, et al. Magnetic resonance imaging of the head in the diagnosis of multiple sclerosis: a prospective 2-year follow-up with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* 1991;41:657–60.