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.

Keywords: magnetic stimulation; multiple sclerosis; transcallosal inhibition

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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 inion line. In the axis of the stimulation coil, the currents were directed anteroposteriorly (induced currents with opposite orientation) because this direction...
is the most effective for eliciting TI. 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. 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. 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. Data were collected with a

![Figure 1](http://jnnp.bmj.com/)

*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 transcortical 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

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Parameter</th>
<th>Normal subjects 50 hands and 50 legs</th>
<th>Limits of normal range</th>
<th>MS patients 100 hands and 100 legs</th>
<th>Limits of normal range</th>
<th>Abnormal responses (muscles/patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>FDI</td>
<td>Central motor latency (ms)</td>
<td>6.7 (1.0)</td>
<td>4.6–9.2</td>
<td>7.3 (1.6)</td>
<td>4.8–12.0</td>
<td>10/7</td>
</tr>
<tr>
<td></td>
<td>Amplitude (mV)</td>
<td>7.6 (1.4)</td>
<td>4.0–10.6</td>
<td>5.7 (2.3)</td>
<td>0.8–10.0</td>
<td>24/17</td>
</tr>
<tr>
<td></td>
<td>Latency of TI (ms)</td>
<td>35.7 (3.2)</td>
<td>29.8–43.0</td>
<td>36.9 (4.5)</td>
<td>27.4–50.4</td>
<td>10/9</td>
</tr>
<tr>
<td></td>
<td>Duration of TI (ms)</td>
<td>24.9 (3.0)</td>
<td>19.6–32.2</td>
<td>34.8 (10.9)</td>
<td>10.6–90.8**</td>
<td>51/36</td>
</tr>
<tr>
<td></td>
<td>Transcallosal conduction time (ms)</td>
<td>15.3 (2.7)</td>
<td>9.0–20.8</td>
<td>15.6 (3.6)</td>
<td>7.0–24.4</td>
<td>2/2</td>
</tr>
<tr>
<td>TA</td>
<td>Central motor latency (ms)</td>
<td>14.2 (2.1)</td>
<td>10.0–19.0</td>
<td>19.0 (5.3)</td>
<td>11.2–33.4**</td>
<td>40/24</td>
</tr>
<tr>
<td></td>
<td>Amplitude (mV)</td>
<td>4.2 (2.2)</td>
<td>1.0–11.6</td>
<td>3.2 (2.1)</td>
<td>0.3–8.3**</td>
<td>3/3</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Contralateral excitatory responses</th>
<th>Transcallosal inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>FDI</td>
<td>22</td>
<td>16*</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Unilateral or bilateral</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Hand and/or leg muscle</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Transcallosal inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unidirectional</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Bidirectional</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Unidirectional or bidirectional</td>
<td>80</td>
</tr>
</tbody>
</table>

*pNo response in one patient. FDI=first dorsal interosseous; TA=tibialis anterior.
Stimulation and recording conditions as described in fig 1. Results of 50 hand muscles of 25 healthy subjects and 100 hand muscles of 50 patients with multiple sclerosis, 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 transcortical inhibitory hand motor responses to 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 lesion score.
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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). 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, the characteristics of impulse propagation in the slowly conducting oligosynaptic or polysynaptic functional system mediating TI are unknown. 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. 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. 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...
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agents. Apart from laboratory supported definite multiple sclerosis, where clinical or paraclinical 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. Hence, MRI as well as visual, auditory, sensory and magnetically evoked motor potentials are used to detect additional lesions. In our study the assessment of TI was auditory, sensory and magnetically evoked investigation of corticospinal tract function by multiple sclerosis than the well established (No. 97–209).

We thank Dr Kerstin Irlbacher, Mrs Kyong-Soo Shin-Nolte and Dr Pascal Grosse for a critical reading of the manuscript. This work has been recommended as a highly sensitive neurophysiological technique in patients suspected of having multiple sclerosis.

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