Motor cortex excitability in focal epilepsies not including the primary motor area—a TMS study

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Summary
It is unclear whether focal epilepsies chronically influence the processing of cortex distant to the epileptogenic zone. Therefore, motor cortex excitability was analysed in patients with temporal and extratemporal epilepsies whose epileptogenic zones did not include the primary motor area. Single and paired-pulse transcranial magnetic stimulation (TMS) was applied to the primary motor cortex in 20 healthy controls and 23 patients with focal epilepsy (39.4 ± 13.2 years; 12 left, 11 right; 14 temporal, nine extratemporal: six frontal, three parieto-occipital) ipsi- and contralateral to the epileptogenic zone. In all patients, the epileptogenic zone did not include the primary motor cortex. The resting motor threshold (RMT), the cortical silent period (CSP), the intracortical inhibition [ICI; combined interstimulus intervals (ISI) 2 and 3 ms] and the intracortical facilitation (ICF; combined ISI 10 and 15 ms) were determined. The measures obtained ipsilateral to the epileptogenic zone were compared with those elicited in contralateral hemispheres and, in exploratory analyses, with controls using non-parametric tests, including Hodges–Lehmann estimates of median differences (HLE) with 95% confidence intervals (CI). In the patient group, the CSP elicited in the ipsilateral motor cortex (median 162.3 ms) was shortened compared with the contralateral CSP (median 174.6 ms; HLE 15.9 ms; CI 6.2, 27.0 ms; P = 0.002). This interhemispheric difference was more pronounced in extratemporal epilepsies (HLE 23.4 ms; CI –3.2, 67.6 ms) compared with temporal epilepsies (HLE 14.3 ms; CI 4.7, 26.2 ms). Patients with parieto-occipital epilepsies showed the greatest interhemispheric differences in CSP (HLE 33.5 ms) and patients with mesial temporal epilepsies the smallest (HLE 9.9 ms). No significant differences were found between ipsi- and contralateral RMT, ICI or ICF. In analyses of subgroups, the CSP was shorter in epileptic hemispheres of patients with extratemporal epilepsies (141.4 ms) than in controls (173.4 ms; HLE 40.0 ms; CI 3.2, 83.4 ms; P = 0.029). ICF was increased in epileptic hemispheres of extratemporal epilepsies (147.6%) compared with temporal epilepsies (114.6%; HLE 33.0%; CI 4.1, 68.3%; P = 0.038). The results suggest that focal epilepsies influence chronically distant cortex, leading to decreased inhibition and increased facilitation in the ipsilateral motor cortex even when the epileptogenic zone is apart from it. This alteration may be due to synaptic reorganization and appears to be more pronounced in extratemporal and neocortical temporal than in mesial temporal epilepsies. This may have diagnostic implications.

Keywords: focal epilepsy; transcranial magnetic stimulation; motor cortex; inhibition; facilitation

Abbreviations: AED = antiepileptic drugs; CI = confidence interval; CSP = cortical stimulation-induced silent period; HLE = Hodges–Lehmann estimate; ICF = intracortical facilitation; ICI = intracortical inhibition; ISI = interstimulus interval; M1 = primary motor cortex; MEP = motor evoked potential; RMT = resting motor threshold; TMS = transcranial magnetic stimulation


Introduction
Epileptogenesis is characterized by heterogeneous pathophysiological processes resulting in an altered balance between excitatory and inhibitory influences at the cortical level (Engel, 1996; Tassinari et al., 2003). In focal epilepsy,
it remains unclear whether these cortical changes are restricted to the epileptogenic zone or extend beyond it and persist during interictal periods.

Multiparametric transcranial magnetic stimulation (TMS) offers the opportunity to separately examine excitatory and inhibitory functions of the motor cortex (M1) in both hemispheres and can therefore be used to detect interictal changes in the primary motor area. Several studies applied TMS to patients with focal epilepsy but revealed conflicting results (Classen et al., 1995; Cincotta et al., 1998, 2000, 2002; Cicinelli et al., 2000; Ertas et al., 2000; Cantello et al., 2000; Werhahn et al., 2000; Shimizu et al., 2001; Kessler et al., 2002; Tassinari et al., 2003). The discrepancies may be due to different stimulation paradigms and the inclusion of heterogeneous patient populations of varying size. In order to gain information on the interictal excitability of the cortex outside the epileptogenic zone, we used multiparametric TMS in a patient population with clearly defined focal epilepsies originating outside the primary motor cortex.

The best methodological approach to investigate focal epilepsy in humans with TMS would be the evaluation of untreated patients. However, this did not seem feasible because of ethical considerations. Therefore, the main focus of this study was on side-to-side differences in the patient group. The basis of assumed interhemispheric differences may rather be the focal epilepsy than treatment with antiepileptic drugs (AEDs), which usually induce bilateral changes (Tassinari et al., 2003).

**Subjects and methods**

**Patients**

Over a 2-year period (2001–2002) we studied consecutively all patients who were admitted to the video-EEG monitoring unit as part of their presurgical epilepsy evaluation and fulfilled the following criteria of eligibility. The inclusion criteria were as follows: diagnosis of focal epilepsy, including unambiguous identification of one epileptogenic zone apart from the primary motor cortex, based on seizure semiology, ictal and interictal video-EEG recordings and high resolution MRI of the brain (Table 1); ongoing seizures defined as at least one seizure per month in the last 6 months; normal neurological examination; right-handedness based on the Edinburgh inventory for the assessment of handedness (Oldfield, 1971); chronic treatment with standard AEDs; and receipt of informed written consent after a detailed explanation of the experimental testing, which had the approval of the local ethics committee. The exclusion criteria were as follows: cardiac pacemaker or vagal nerve stimulator; a history of previous neurosurgery; and seizure in the last 24 h before testing.

Using these criteria, 23 patients were included in the study (39.4 ± 13.2 years; focal epilepsy, 12 left, 11 right; 14 temporal, 9 frontal).

**Table 1 Clinical characteristics of patients**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Epilepsy syndrome</th>
<th>Side</th>
<th>Aetiology</th>
<th>Duration of epilepsy (years)</th>
<th>Seizure frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Medication&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Outcome after surgery&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
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<td>Dysplasia</td>
<td>9</td>
<td>15</td>
<td>CBZ, TPM</td>
<td>II</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>F</td>
<td>mTLE</td>
<td>Right</td>
<td>HS</td>
<td>29</td>
<td>6</td>
<td>CBZ, GBP</td>
<td>IA</td>
</tr>
<tr>
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<td>24</td>
<td>F</td>
<td>FLE</td>
<td>Right</td>
<td>–</td>
<td>9</td>
<td>12</td>
<td>CBZ, LEV, TPM</td>
<td>Not operated</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>neoc. TLE</td>
<td>Left</td>
<td>Ganglioglioma</td>
<td>10</td>
<td>3</td>
<td>CBZ</td>
<td>Not operated</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>F</td>
<td>PLE</td>
<td>Left</td>
<td>Dysplasia</td>
<td>3</td>
<td>5</td>
<td>CBZ, TPM</td>
<td>IA</td>
</tr>
<tr>
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<td>Left</td>
<td>Post-traumatic</td>
<td>11</td>
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<td>IA</td>
</tr>
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<td>–</td>
<td>15</td>
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<tr>
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<td>59</td>
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<td>mTLE</td>
<td>Right</td>
<td>HS</td>
<td>26</td>
<td>9</td>
<td>LEV, PHT</td>
<td>IA</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
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<td>mTLE</td>
<td>Left</td>
<td>HS</td>
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<td>CBZ, LEV</td>
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</tr>
<tr>
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<td>38</td>
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<td>POLE</td>
<td>Right</td>
<td>Ganglioglioma</td>
<td>21</td>
<td>4</td>
<td>CBZ, LEV</td>
<td>IA</td>
</tr>
<tr>
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<td>Left</td>
<td>–</td>
<td>25</td>
<td>2</td>
<td>LEV</td>
<td>Not operated</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>F</td>
<td>neoc. TLE</td>
<td>Left</td>
<td>–</td>
<td>11</td>
<td>15</td>
<td>CBZ, LTG</td>
<td>Not operated</td>
</tr>
<tr>
<td>13</td>
<td>54</td>
<td>M</td>
<td>mTLE</td>
<td>Right</td>
<td>HS/dysplasia</td>
<td>50</td>
<td>10</td>
<td>CBZ, LEV</td>
<td>IA</td>
</tr>
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<td>41</td>
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<td>Left</td>
<td>HS</td>
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<td>3</td>
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<tr>
<td>16</td>
<td>49</td>
<td>M</td>
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<td>Left</td>
<td>HS</td>
<td>45</td>
<td>4</td>
<td>CBZ, LEV, LTG</td>
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</tr>
<tr>
<td>17</td>
<td>34</td>
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<td>FLE</td>
<td>Right</td>
<td>Cystic lesion</td>
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<td>20</td>
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<td>56</td>
<td>M</td>
<td>mTLE</td>
<td>Left</td>
<td>HS</td>
<td>56</td>
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<td>LTG, OXC</td>
<td>IA</td>
</tr>
<tr>
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<td>Right</td>
<td>HS</td>
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<td>LEV, OXC</td>
<td>IA</td>
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</tr>
<tr>
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<td>FLE</td>
<td>Right</td>
<td>–</td>
<td>3</td>
<td>1</td>
<td>LTG, VPA</td>
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<tr>
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<td>30</td>
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<td>FLE</td>
<td>Left</td>
<td>Dysplasia</td>
<td>18</td>
<td>30</td>
<td>OXC, TPM</td>
<td>Not operated</td>
</tr>
<tr>
<td>23</td>
<td>19</td>
<td>M</td>
<td>FLE</td>
<td>Right</td>
<td>Ganglioglioma</td>
<td>5</td>
<td>20</td>
<td>LEV, OXC</td>
<td>IA</td>
</tr>
</tbody>
</table>

F = female; FLE = frontal lobe epilepsy; HS = hippocampal sclerosis; M = male; PLE = parietal lobe epilepsy; POLE = parieto-occipital epilepsy; neoc. TLE = neocortical temporal lobe epilepsy; mTLE = mesial temporal lobe epilepsy. *Seizure frequency given as mean seizure frequency per month. CBZ = carbamazepine; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PRM = primidone; PHT = phenytoin; TPM = topiramate; VPA = valproate. *Outcome according to Engel’s classification (Engel et al., 1993).
nine extratemporal: six frontal, three parieto-occipital; mean laterality score in the Edinburgh inventory for the assessment of handedness: 91.3 ± 16.4). Further characteristics are given in Table 1. In 18/23 patients (78%), an epileptogenic lesion outside M1 could be identified on MRI scans. The EEG data confirmed the location of the assumed epileptogenic zone in every case. Two of the five remaining patients with negative MRI suffered from left temporal lobe epilepsy with complex partial seizures, with automatisms accompanied by left temporal seizure patterns in EEG recordings. Patient 3 suffered from right frontal lobe epilepsy with normal MRI and showed short complex partial seizures with hypermotor signs but no focal clonic or tonic symptomatology or falls (Table 1). The ictal EEG revealed right frontal seizure patterns. Right frontal spike–wave complexes with secondary bilateral synchrony were recorded interictally. Patient 7, diagnosed with MRI-negative, left parieto-occipital epilepsy, experienced visual auras on the right which were followed at times by right-sided acoustic auras and complex partial seizures. The ictal EEG showed a non-lateralized seizure pattern at the beginning which evolved to a left temporal seizure pattern late during the course of the clinical seizure. Patient 21, diagnosed with right frontal lobe epilepsy, had a normal MRI and suffered from auras consisting of a strange feeling in her head and bilateral cephalic parasthesias which were followed by short complex partial seizures, sometimes including forceful version of the head to the left. The seizures tended to occur in clusters and were accompanied by right frontotemporal seizure patterns in the EEG.

Eleven patients (48%) underwent epilepsy surgery, which confirmed the preoperative diagnosis. Nine of these patients remained completely seizure-free postoperatively (Table 1). One patient suffered postoperatively only from rare auras and another patient, who had left temporal lobe epilepsy with normal MRI, experienced an 80% reduction in seizure frequency after mesial temporal lobectomy on the left.

Twenty right-handed healthy volunteers of similar age to the patient group served as controls (11 women; 27.8 ± 5.8 years; mean laterality score in the Edinburgh inventory for the assessment of handedness: 88.9 ± 10.8). None of the controls had a history of a neurological illness or was on medication at the time of the study. The subjects were instructed not to take any neuro- or psychoactive drugs, including alcohol, for at least 24 h before testing.

**Methods**

Motor evoked potentials were recorded using surface EMG Ag–AgCl electrodes placed over the abductor digiti minimi muscle in a belly–tendon montage. The EMG raw signal was amplified, bandpass-filtered (20 Hz to 40 kHz) and recorded on a PC using data collection and averaging software (Magstim®; Center for Sensorimotor Research, Munich, Germany) for offline analysis. TMS was delivered through a focal figure-of-eight magnetic coil (90 mm external diameter) connected to two magnetic stimulators via a BiStim-module (all Magstim®; Whitland, UK). Subjects were seated in an armchair with the head fixed in a plastic foam headrest. The coil was placed flat on the skull over the motor cortex contralateral to the EMG leads at the optimal site for contralateral abductor digiti minimi muscle activation with the current induced flowing from posterior to anterior approximately perpendicular to the assumed line of the central sulcus (Mills et al., 1992). The coil position was marked directly on the scalp to ensure accurate coil repositioning. In all double pulse procedures, the interval between trials was randomly changed between 4 and 6 s and in single-pulse procedures between 8 and 10 s by the computer system.

**Measures of motor cortex excitability**

The following TMS measures were used to investigate motor cortex excitability.

The resting motor threshold (RMT) was defined as the minimal stimulus intensity required to induce a motor evoked potential (MEP) of more than 50 μV peak-to-peak amplitude in at least five out of 10 consecutive trials. Complete muscle relaxation was monitored via audiovisual feedback. A step width of 1% of maximal stimulator output was used for determination of the RMT.

Intracortical inhibition (ICI) and facilitation (ICF) were obtained at short interstimulus intervals (ISI) of 2 and 3 ms (ICI) and longer interstimulus intervals of 10 ms and 15 ms (ICF), respectively, using a protocol described previously (Kujirai et al., 1993; Werhahn et al., 1999; Reis et al., 2002). The conditioning stimulus was set to an intensity of 75% of RMT, which produces no changes in excitability in the spinal cord (Kujirai et al., 1993; Ziemann et al., 1996; DiLazzaro et al., 1998; Ilic et al., 2002). The intensity of the following suprathreshold test stimulus was adjusted to produce MEPs of an approximately 1.5 mV peak-to-peak amplitude at rest. Fifteen trials of single control test stimuli and 15 paired stimuli of each ISI were recorded, generated in random order by the computer program. The average of the 15 trials was used to define the amplitude of the peak-to-peak MEP. The conditioned response was defined as the mean amplitude of the conditioned responses belonging to each ISI, expressed as percentage of the mean amplitude of the unconditioned test response.

The resting motor threshold was above 70% of the maximal stimulator output in both hemispheres of five patients (patients 9, 10, 13, 15 and 18) and in the left hemisphere ipsilateral to the epileptogenic zone in patient 7. Therefore, the paired pulse paradigm could not be performed in these hemispheres because the stimulus intensity generating an MEP of 1.5 mV peak-to-peak-amplitude reached more than 90% of the maximal stimulator output, which was not tolerated by one patient and led to constant overheating of the coil in the other cases.

The cortical stimulation-induced silent period (CSP) was measured in 10 trials at a stimulus intensity of 110% of the RMT. The subjects were instructed to hold a voluntary muscle contraction of approximately 30% of the maximal force, controlled by audiovisual feedback. The CSP duration was defined in individual trials as the interval from the beginning of the stimulus-induced MEP to the first recurrence of voluntary EMG activity displayed at high magnification. The CSP duration was determined by a single investigator (H.M.H.), who was blinded to the diagnosis of the patients.

In each subject, both motor cortices were evaluated separately in the above-mentioned fashion. The two sessions were separated by a break of 30 min. Both tests were performed in a randomized order by one of the authors (J.R.), who was blinded to the diagnosis of the patients.

**Statistical analysis**

For the purpose of this study, the ipsilateral and contralateral motor cortex or hemisphere was defined as the motor cortex or hemisphere located ipsilaterally or contralaterally to the epileptogenic zone. The four parameters RMT, ICI, ICF and CSP of each hemisphere.
Table 2 TMS data for ipsilateral and contralateral patients’ hemispheres and for controls

<table>
<thead>
<tr>
<th></th>
<th>RMT (%)</th>
<th>ICI (%)</th>
<th>ICF (%)</th>
<th>CSP (ms)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (25, 75% quartiles)</td>
<td>n</td>
<td>Median (25, 75% quartiles)</td>
</tr>
<tr>
<td>Ipsilateral hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>23</td>
<td>50 (45, 58)**</td>
<td>17</td>
<td>45.7 (36.7, 72.4)</td>
</tr>
<tr>
<td>Temporal epilepsies</td>
<td>14</td>
<td>49.5 (46, 58)</td>
<td>11</td>
<td>50.9 (29.7, 72.9)</td>
</tr>
<tr>
<td>Extratemporal epilepsies</td>
<td>9</td>
<td>51.5 (45, 66.5)</td>
<td>6</td>
<td>45.7 (40.2, 72.4)</td>
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<tr>
<td>Contralateral hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>49 (46, 56)**</td>
<td>18</td>
<td>62.1 (42.5, 70.3)</td>
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<tr>
<td>Temporal epilepsies</td>
<td>14</td>
<td>48.5 (46, 53)</td>
<td>11</td>
<td>62.1 (57, 75.9)</td>
</tr>
<tr>
<td>Extratemporal epilepsies</td>
<td>9</td>
<td>50.5 (46, 60.5)</td>
<td>7</td>
<td>60.4 (42.5, 64.8)</td>
</tr>
<tr>
<td>Controls</td>
<td>20</td>
<td>39.5 (38, 45.5)</td>
<td>20</td>
<td>61.4 (46.0, 67.0)</td>
</tr>
</tbody>
</table>

**P < 0.01; *P < 0.05.

In the control group so that the side (left or right) of the hemisphere harbouring the epileptogenic zone was not accounted for in the statistical analyses of the patient group.

In the patient group, the CSP elicited in the ipsilateral motor cortex was shortened compared with the contralateral CSP (HLE 15.9 ms; CI 6.2, 27.0 ms; P = 0.002; n = 23; Table 2, Figs 1 and 2). This interhemispheric difference was more pronounced in extratemporal epilepsies (HLE 23.4 ms; CI −3.2, 67.6 ms; P = 0.11; n = 9) compared with temporal epilepsies (HLE 14.3 ms; CI 4.7, 26.2 ms; P = 0.01; n = 14; Table 2). The three patients with parietal or parieto-occipital epilepsies showed the greatest interhemispheric differences in CSP (HLE 33.5 ms; CI 55.20, ∞; P = 0.65). The lowest estimate of median differences was found in patients with mesial temporal epilepsies (HLE 9.9 ms; CI −9.4, 29.4 ms; P = 0.19; n = 8). Frontal (HLE 12.5 ms; CI −23.9, 107.4 ms; P = 0.63; n = 6) and neocortical temporal lobe epilepsies (HLE 21.1 ms; CI 7.1, 41.9 ms; P = 0.03; n = 6) showed only moderate interhemispheric CSP differences. Resting motor thresholds (HLE 1.0%; CI −1.5, 3.5%; P = 0.34; n = 23), ICI (HLE −7.2%; CI −17.3, 3.1%; P = 0.16; n = 17) and ICF (HLE −6.5%; CI −28.8, 10.4%; P = 0.71; n = 17) did not show significant differences between epileptic and non-epileptic hemispheres (Table 2, Fig. 2).

Comparing the entire patient group with controls in explorative analyses, a trend was seen towards shorter CSP in ipsilateral (HLE 14.3 ms; CI −3.8, 39.4 ms; P = 0.12; Fig. 2) but not in contralateral hemispheres (HLE 0.64 ms; CI −16.9, 20.0 ms; P = 0.64). In the epileptic hemispheres of patients with extratemporal epilepsies, the CSP was markedly reduced compared with controls (HLE 40.0 ms; CI 3.2, 83.4 ms; P = 0.029). This was not the case in non-epileptic hemispheres of this subgroup (HLE 13.2 ms; CI −13.2, 45.4 ms; P = 0.35) and in either hemisphere of patients with temporal epilepsies (ipsilateral: HLE 6.3 ms; CI −14.8, 25.5 ms; P = 0.59; contralateral: HLE 15.1 ms; CI −3.4, 35.6 ms; P = 0.10; Table 2). In the patient group, the neurological parameters and the side (left or right) of the hemisphere harbouring the epileptogenic zone were used for inter- and intra-individual comparisons. For each parameter, one single value per hemisphere was calculated by averaging the values obtained by ISI 2 and 3 ms for each patient and ICF was defined as the average of the values of ISI 10 and 15 ms. In further exploratory analyses, the patient group was divided into subgroups according to the exact location of the epileptogenic zone. These subgroups contained only small patient numbers and were of varying size. Therefore, the emphasis of the statistical evaluation of these subgroups was laid on the descriptive measures for estimation of effect sizes, such as the HLE with CI, rather than on P-values, which were also provided.

The TMS data of the hemispheres ipsilateral and contralateral to the epileptogenic zone were separately compared with the control group. The averaged TMS measures from the left and right hemispheres of each control subject were used as control data. For inter-individual comparisons, the Wilcoxon–Mann–Whitney test and HLE were used. In addition, the non-parametric correlation coefficient Spearman’s r was applied in further analyses. The level of significance of each of the exploratory comparisons was set at 0.05.

Results

There were no significant differences comparing the measures obtained by ISI 2 ms to ISI 3 ms and ISI 10 ms to ISI 15 ms in either hemisphere of the patient group. In respect to the four parameters evaluated in this study, there were no significant differences between left and right hemispheres in the control group so that the side (left or right) of the hemisphere harbouring the epileptogenic zone was not accounted for in the statistical analyses of the patient group.
Fig. 1 Individual TMS measures elicited in patients’ hemispheres ipsi- and contralateral to the epileptogenic zone. Temporal = patient with temporal epileptogenic zone; extratemp. = patient with extratemporal epileptogenic zone.

Fig. 2 TMS measures elicited in patients’ hemispheres ipsilateral (ipsilat.) and contralateral (contralat.) to the epileptogenic zone and in controls. ICI, ICF as a percentage of mean amplitude of unconditioned test response; RMT as a percentage of maximal stimulator output; CSP in ms; *P < 0.01.
ipsilateral and contralateral RMT were elevated compared with controls ($P < 0.001$ for each side; Table 2, Fig. 2). The ICI and ICF on both sides were not significantly altered compared with controls (Table 2, Fig. 2).

Intracortical facilitation was increased in epileptic hemispheres of extratemporal epilepsies compared with temporal epilepsies (HLE 33.0%; CI 4.1, 68.3%; $P = 0.038$; Table 2, Fig. 1). The difference was similar comparing the contralateral hemispheres of both subgroups (HLE 31.7%; CI −2.6, 49.5%; $P = 0.062$; Table 2). The RMT, ICI and CSP were not significantly different between extratemporal and temporal epilepsies in both hemispheres.

There was no significant correlation of duration of epilepsy or seizure frequency with RMT, ICI, ICF or CSP of both hemispheres of the patient group. Whether or not the patients suffered from secondarily generalized tonic–clonic seizures (13 with and 10 without generalized tonic–clonic seizures) did not influence the differences in TMS measures between epileptic and non-epileptic hemispheres.

**Discussion**

In the present study, the interictal excitability of the motor cortex was evaluated in a patient population with clearly defined focal epilepsies of varying aetiologies which originated outside the primary motor cortex. Shortened CSP was found in M1 ipsilateral to the epileptogenic zone compared with contralateral hemispheres, indicating interhemispheric asymmetry in motor cortex inhibition. This finding was more pronounced in extratemporal and neocortical temporal than in mesial temporal epilepsies. In addition, ICF appeared to be increased in extratemporal epilepsies compared with temporal epilepsies in epileptic and similarly in non-epileptic hemispheres.

**Pathophysiological interpretation: cortical silent period**

Studying non-epileptic patients with focal brain lesions, the damage in M1 induced a shortening of the CSP while a lesion of brain areas outside M1 was followed by CSP prolongation (von Giesen et al., 1994). This remote effect of structural lesions on the primary motor cortex was interpreted as disinhibition of inhibitory cortical interneurons. The opposite behaviour was found in focal epilepsies. When the epileptogenic zone included M1, several studies found the CSP to be prolonged, suggesting upregulation of inhibitory neurotransmission in this area (Classen et al., 1995; Cincotta et al., 1998, 2002). In contrast, the lateralizing asymmetry of the CSP in our study suggested decreased inhibitory influences in the motor cortex when M1 was not part of the epileptogenic zone. These findings support the view that an epileptogenic process in M1 activates inhibitory interneurons in this area while epilepsies outside M1 stimulate pathways which lead to inhibition of these interneurons and thus to disinhibition of M1. The present study revealed the greatest interhemispheric alteration of the CSP in parieto-occipital epilepsies, moderate differences in neocortical temporal and frontal epilepsies and the smallest interhemispheric variation in mesial temporal epilepsies. This gradient may reflect more abundant intercortical connections of M1 with extratemporal and neocortical temporal than mesial temporal regions.

The silent period is assumed to originate in its later phase from activation of intracortical inhibitory, possibly GABAergic interneurons (Cicinelli et al., 2000), which may also play an important role in focal motor seizures (Hamer et al., 2003). It could be hypothesized that the interictally increased inhibition of these interneurons suggested by the present study facilitates seizure propagation outside the seizure onset zone or may even play a role in secondary epileptogenesis (Morrell, 1985; Cibuła and Gilmore, 1997). There was no indication that different aetiologies caused specific alterations of TMS parameters. However, this was not systematically studied because of the small numbers of patients who suffered from each aetiology. The major pathologies, such as tumour or dysplasia, were found in frontal, parieto-occipital and temporal epilepsies in this study, which supports the assumption that the location of the epileptogenic zone influenced the appearance of the remote effects.

Several studies applied TMS to patients with focal epilepsy but revealed conflicting results (Classen et al., 1995; Cincotta et al., 1998, 2000, 2002; Cicinelli et al., 2000; Ertas et al., 2000; Cantello et al., 2000; Werhahn et al., 2000; Shimizu et al., 2001; Kessler et al., 2002; Tassinari et al., 2003). This may be due to the heterogeneity of these studies so that many reports are not easily comparable to the present evaluation. Several studies reported only a few cases (Classen et al., 1995; Cincotta et al., 2000, 2002; Shimizu et al., 2001). Others used a flat round coil centred on the vertex for TMS (Cincotta et al., 1998, 2000; Cantello et al., 2000) or did not examine separately epileptic and non-epileptic hemispheres in epilepsies that did not include M1 (Cincotta et al., 1998). In some studies, only special subgroups of patients were investigated, such as patients with poststroke seizures (Kessler et al., 2002) or cortical dysgenesis (Cincotta et al., 2000). Other reports did not clearly differentiate between patients with epileptogenic zones including or excluding the primary motor area (Cicinelli et al., 2000; Cantello et al., 2000; Werhahn et al., 2000) or even included patients with focal and generalized epilepsies (Ertas et al., 2000). Therefore, in order to gain information on the interictal excitability of cortex distant to the epileptogenic zone, we applied multiparametric TMS in a patient population with clearly defined focal epilepsies excluding M1. Similarly to our results, a study of 16 patients with focal epilepsies found a shorter CSP duration stimulating the hemisphere containing the focal epilepsy, although the authors did not differentiate between temporal and extratemporal epilepsies and it was left open whether M1 was included in the epileptogenic zone in a subset of patients (Cicinelli et al., 2000). Two other studies including patients with central and extracentral epilepsies
did not find significant changes in CSP (Cantello et al., 2000; Werhahn et al., 2000).

**Intracortical facilitation**

Compared with patients with temporal epilepsies, patients with extratemporal epilepsies showed an apparent increase in ICF in epileptic and non-epileptic hemispheres. It is hypothesized that especially extratemporal epileptogenic processes stimulate ipsi- and also contralaterally excitatory interneurons beyond the epileptogenic zone in addition to inhibition of inhibitory interneurons, because ICF is thought to represent activation of excitatory, possibly glutamatergic interneurons beyond the epileptogenic zone, reflected in decreased CSP and increased ICF. Further studies are needed to decide whether these TMS findings may be of clinical help in lateralizing or localizing the epileptogenic zone.

A previous study used cluster analysis to find similar bilaterally increased facilitation in a smaller subgroup of patients with focal epilepsy, but differences between temporal and extratemporal epilepsies were not established (Cantello et al., 2000). In contrast, another study reported decreased ICF in both hemispheres of 13 untreated patients with focal epilepsy compared with controls (Werhahn et al., 2000). This study did not exclude epilepsies involving the primary motor cortex and separate comparisons of temporal and extratemporal epilepsies versus controls were not reported. This may have contributed to the different findings compared with the present study, which found ICF to be less pronounced only in temporal epilepsies and increased in extratemporal epilepsies compared with controls. The differences, however, did not reach statistical significance.

**Anticonvulsant medication**

Using single-pulse TMS, the present results revealed an increase in resting motor threshold in epileptic and non-epileptic patients’ hemispheres compared with controls. This elevation was very probably due to the chronic anticonvulsant medication of the patients, confirming previous studies (Hufnagel et al., 1990; Michelucci et al., 1996; Cantello et al., 2000; Tassinari et al., 2003). Drugs affecting ion channel function were especially effective in raising motor thresholds (Ziemann et al., 1996) and most patients in the present study were taking such drugs. Motor thresholds were normal in untreated patients with focal epilepsy (Michelucci et al., 1996) and in a group of patients with focal epilepsy who discontinued the AED at least 48 h prior to the TMS evaluation (Werhahn et al., 2000).

It is unlikely that the unilaterally decreased CSP and increased ICF found in this study population were due to chronic intake of AEDs because AEDs, if at all, tend to cause bilateral increases in CSP and decreases in ICF (Tassinari et al., 2003). It cannot be excluded that AED administration prohibited more pronounced alterations and prevented us from finding further differences between the patient and control groups.

**Conclusions**

The present study suggests that focal epilepsies influence chronically distant cortex. These remote effects lead to persistent hyperexcitability of ipsilateral motor cortex beyond the epileptogenic zone, reflected in decreased CSP and increased ICF. Further studies are needed to decide whether these TMS findings may be of clinical help in lateralizing or localizing the epileptogenic zone.

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**References**


