The motor syndrome associated with exaggerated inhibition within the primary motor cortex of patients with hemiparetic stroke

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Summary
Following transcranial magnetic stimulation (TMS) at stimulation strength of 1.5 times the resting motor threshold, a silent period (SP) of ~180 ms duration can be observed in surface EMG-registrations of tonically activated small hand muscles. This SP is believed to be generated cortically and can be prolonged in stroke patients, but it is not known whether a prolongation of the SP has any functional significance. In order to answer the question of whether enhanced cortical inhibition can contribute to pathophysiology of motor dysfunction we studied stroke patients with clearly prolonged SP durations in the first dorsal interosseus muscle (>2 times that of the intact side), but with normal magnetically evoked motor potentials. Sixteen patients out of a cohort of 174 consecutive patients presenting with acute hemiparetic stroke fulfilled the inclusion criteria. Serial TMS investigations were performed for up to 2 years post-stroke. In all patients, the SP duration decreased in parallel with clinical improvement. In two patients, intermittent clinical deterioration was accompanied by an increase in the SP duration. In four patients, in addition to a markedly prolonged SP duration, the phenomenon of a complete inability to initiate voluntary muscle activity for several seconds, following TMS, could be observed in a number of trials (‘motor arrest’). Detailed clinical analysis revealed that, in addition to hemiparesis, distinct motor disturbances in patients with SP prolongation could be observed. These motor disturbances resembled those of motor neglect and were characterized by motivationally dependent under-utilization of the affected arm, impairment of movement initiation, inability to maintain a constant force level and to scale forces, and impairment of individual finger movements. In 12 of the 16 patients at least one additional behavioural manifestation of neglect was present. We suggest that in stroke patients severe motor dysfunction may be caused by hyperactivity of cortical inhibitory interneurons rather than by direct lesions of descending motor tracts. Cortical hyperinhibition may, in turn, result from damage to any of a number of afferent pathways to the motor cortex which modulate local interneuronal activity.

Keywords: motor neglect; paresis; motor syndrome; transcranial magnetic stimulation; silent period

Abbreviations: FDI = first dorsal interosseous (muscle); MEP = motor evoked potential; MI = primary motor cortex; PT = pyramidal tract; SP = silent period; TMS = transcranial magnetic stimulation

Introduction
It is common clinical knowledge that acute hemiparesis can result from lesions of the contralateral primary motor cortex (MI) or of the pyramidal tract (PT) at a subcortical level, at the capsular, medullary or the spinal cord level. In lesions of the internal capsule a severe paresis occurs when the posterior limb is affected (Fries et al., 1993). In daily clinical practice central paresis does not occur as an isolated phenomenon but is often combined with spasticity, loss of dexterity and release of flexor reflexes. The paresis is usually attributed to the lesion of the PT itself, whereas the other symptoms of the upper motor syndrome are thought to result from lesions of other descending motor pathways in the vicinity of the PT or to be an expression of the functional disturbance of systems modified by PT collaterals. The
importance of the PT for normal motor function has been underlined by a number of studies in stroke patients employing transcranial electrical or magnetic stimulation of the primary motor cortex (Berardelli et al., 1987; Macdonnel et al., 1989; Dominkus et al., 1990; Berardelli et al., 1991; Ferbert et al. 1992; Tsai et al., 1992; Heald et al., 1993a, b; Binkofski et al., 1996). As a rule there is a good correlation between the severity of the hemiparesis and the damage to the PT as judged by the latency and amplitude of the early evoked EMG response (MEP).

However, it is known from clinical studies (Hömberg et al., 1991; Netz and Hömberg, 1992; Seitz et al., 1994) that in individual cases a severe motor deficit can exist while the MEPs are completely normal. In addition to lesions of the MI, lesions of the supplementary motor area (Schneider and Gauthier, 1994), the lateral premotor cortex (Freund and Hummelsheim, 1985; Schneider and Gauthier, 1994), which cannot be tested by transcranial magnetic stimulation (TMS) can also result in severe contralateral paresis. Paresis associated with supplementary motor area lesions and lateral premotor cortex lesions may still indicate an involvement of the PT because these areas contribute to the PT (Dum and Strick, 1991). Alternatively, paresis associated with such lesions may result from functional involvement of the MI induced indirectly by lack of afferent inflow from these areas to the PT neurons within the MI. A similar explanation may be used for paresis resulting from lesions of the thalamus (Seitz et al., 1994; Schneider and Gauthier, 1994; Kunesch et al., 1995) and the parietal cortex (Kunesch et al., 1995).

Recently, evidence was presented that lesions in the thalamus, premotor and parietal cortex, but sparing the MI, produce remote neurophysiological effects within the MI (Giesen et al., 1994a). In this study, TMS was used to investigate inhibitory actions within the motor cortex. The authors analysed the period of electrical silence (SP) following the early excitatory response in the surface EMG after TMS, which is believed to be of cortical origin (Roick et al., 1993; Wilson et al., 1993; Schnitzler and Benecke, 1994). Von Giesen et al. (1994a) showed that the SP was shortened when the MI was affected in isolation whereas the SP was prolonged when the lesion was located outside the MI including lesions with a subcortical location; prolongation of the SP was detected while the MEPs were fully preserved supporting the morphological evidence derived from structural findings that the PT had remained intact. The results of von Giesen et al. (1994a) suggested that interneuronal inhibition within the primary motor cortex is modulated by cortical and subcortical areas anatomically projecting to the MI. Furthermore it was shown by studies employing conditioning electrical or magnetic stimulation that intracortical inhibition can be modulated transcallosally and cortico-cortically (Ferbert et al., 1992; Kujirai et al., 1993; Classen et al., 1995a; Schnitzler et al., 1996). In the present study we investigated the hypothesis that one mechanism producing substantial motor deficits in stroke patients is an excessive cortical inhibition of PT cells.

Patients and methods

Patients

One hundred and seventy-four patients presenting with acute motor stroke over a period of 2 years were assessed for inclusion in the study. Patients were included in the study if they fulfilled the following criteria: (i) an acutely presenting motor syndrome; (ii) the SP duration in the contralesional surface EMG was $\geq 2 \times$ that on the intact side; (iii) central motor latencies and MEPs were within normal limits as defined previously in our laboratory (Kloten et al., 1992).

At a given stimulus intensity, the SP duration in healthy normals increases slightly (by 20–30 ms) when measured at a force level of <5% of the maximum (Cantello et al., 1992) and remains essentially constant above 5% of maximal voluntary force production (Roick et al., 1993). Insufficient force production resulting from stroke could potentially lead to a prolongation of the SP on the paretic side. To account for this factor we considered a prolongation of $\geq 2$ times that on the intact side as abnormal.

Patients were investigated by serial TMS. Of the 174 patients assessed, 16 met the criteria and were entered into the trial. The patients had a mean age ($\pm$SD) of 62 $\pm$ 13 years. Eight patients were male and eight were female. One additional patient was also investigated serially while being treated for cerebral lymphoma.

The first investigation was performed within 1 week of presentation with two exceptions (W.A. and S.V.) in whom TMS was performed in the second week. This stage is referred to as the acute stage. Serial investigations (3.8 $\pm$ 1.5, mean $\pm$ SD; range 2–7 weeks) were performed during the period of dynamic alterations of motor function at appropriate intervals. In 10 patients the last TMS study was carried out between 90 days and 2 years after the initial one. This stage is referred to as the chronic stage. If the patient was unable to produce any voluntary motor activity thresholds in the initial investigation, central motor latencies and relative cortical amplitudes relevant for the inclusion criteria were in those cases taken from the first TMS study when voluntary muscle activation had returned to some degree and an SP could be determined.

In addition to the patients, silent periods elicited by TMS using the same standard protocol as described below were also performed in 16 age- and sex-matched healthy control subjects. Mean age of the control group was 60 $\pm$ 15 years. Informed consent was obtained from all patients and control subjects and the study received approval from the Ethical Committee of the University of Düsseldorf.

Stimulation

The patients were seated comfortably in a semireclined armchair. TMS was performed with a conventional circular
coils (outer diameter 12 cm) connected with a Magstim 200 (Madaus, Freiburg, Germany). The stimulus intensity was set to 1.5 times the threshold of relaxed muscle. Threshold was defined as the stimulus intensity which induced a response signal of \( \geq 50 \mu V \) in the relaxed target muscle in three of six consecutive trials. Motor threshold was chosen as the stimulus intensity reference because it is far more easy and faster to obtain in patients than the SP threshold. For preferential stimulation of the right or left arm-associated motor cortex, the coil was held flat over the vertex and clockwise or anticlockwise current flow was used, respectively.

In two patients, a conditioning-test stimulus paradigm was applied. Details of the experimental procedure have been described previously (Roick et al., 1993). Briefly, conditioning and test stimuli were delivered (interstimulus intervals of 500 and 1000 ms) through the same circular coil connected to a Novametrix Bistim device used in combination with two Novametrix Magstim 200 stimulators. Conditioning stimulus intensity was set to 1.5 times threshold intensity (as measured using the Bistim device) and test stimulus intensities were 1.2 times or 1.5 times threshold.

**Recording and evaluation**

The surface EMG was recorded from the first dorsal interosseous (FDI) muscle. EMG-signals were recorded by disposable Dantec surface electrodes, amplified using a Toennies Myograph IIR with bandpass filtering between 20 and 3000 Hz. Potentials were digitized at a frequency of 5 kHz using a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK) with standard software. Data were stored on a changeable hard disk for later off-line analysis. Responses were obtained while the patients maintained a slight voluntary contraction (20% of maximal force). The duration of the SP was defined as the time interval from stimulus delivery to the return of voluntary activity (Triggs et al., 1992). Ten trials were analysed for the evaluation of MEP responses and SP durations.

Amplitudes were measured peak-to-peak. In order to account for differences of maximal amplitudes after peripheral (i.e. ulnar nerve) electrical stimulation, relative MEP amplitudes were calculated by dividing the amplitude after TMS by the amplitude after supramaximal peripheral electrical stimulation (M-response) of the FDI. Latency was defined as the time from stimulus delivery to the beginning of the response potential and the smallest value out of the ten measurements was taken. Central motor latencies were calculated by subtracting the latency after magnetic root stimulation from the latency after cortical stimulation.

The MEP amplitude from the affected side was considered abnormal if it was \(< 15\%\) of the M-response of the FDI or if the relative amplitude (see above) was \(< 50\%\) of the relative amplitude of the intact side (Kloten et al., 1992). The central motor latency was considered abnormal when it exceeded the normal range as defined in previous investigations (i.e. if it was \(> 7.8 \mu V\) in patients <60 years of age or \(> 8.7 \mu V\) in patients \(\geq 60\) years of age) or if the difference between the latencies of both sides was \(> 1.5 ms\) (Kloten et al., 1992).

In the double stimulation paradigm, with a test stimulus of 1.5 times threshold, the MEP amplitudes were expressed as percentages of the responses to the conditioning stimulus (1.5 times threshold). With a test stimulus of 1.2 times threshold the MEP amplitudes were expressed, for comparison, as percentages of unconditioned responses following stimuli of 1.2 times threshold obtained directly before the conditioning-test stimulus experiment.

**Force and kinematic recordings**

In four patients a semi-quantitative standardized investigation of various simple motor tasks was performed while the EMG was recorded from the FDI (both on the affected and on the intact side).

In the first investigation, the patients had to tap the index finger on the table at their preferred speed and as regularly as possible. In the second investigation, the patients had to abduct their index finger as steadily as possible against a firm resistance with the hand lying flat on the table for a period of 5 s after a verbal command was given. In the third investigation, the patients had to accomplish two tasks by abducting their index finger against a strain gauge (range 0–100 N, non-linearity <1\%, contact surface area 0.7×1.8 cm²) mounted firmly on the table with their hand flat on the table. In this investigation, visual feedback of the force level was provided to the patients on an oscilloscope screen ~40 cm in front of the patients. In task A, they had to produce their individual maximal force and to keep it as constant as possible over a period of 5 s. This task was also used to compare rise-time to reach peak force in the affected and the unaffected FDI. In task B, patients had to match 10% of their maximal force as determined in the first task.

**Definition of lesion**

Lesions as visible on MRI or CT images were plotted on the corresponding templates from the anatomical atlas of Matsui and Hirano (1978) for anatomical localization. Wherever possible, images obtained during an early chronic stage (4 weeks and later) were evaluated.

**Statistical analysis**

Statistical analysis was done using one-tailed paired \( t \) tests for comparisons between the affected and unaffected sides, of relative MEP-amplitudes, latencies, motor thresholds and SP durations, and simple \( t \) tests were used for comparisons between patients and age-matched control subjects. Paired two-tailed \( t \) tests were employed for comparisons between acute and chronic stages and when conditioned test responses were compared with single pulse evoked responses obtained
dominance and a proximo-distal gradient, especially evident in the upper extremity. Six cases had a complete hemiplegia which improved within 2–14 days and then resembled the other 10 patients in the distribution of the paresis. Post-stroke four out of 16 patients showed an initial conjugate deviation (of the eyes) towards the unaffected side. Peak isometric force production, as measured clinically with a vigorimeter and a strain gauge, was reduced. Individual finger movements were impossible or severely impaired. Distal isotonic movements such as index tapping or alternating finger movements were slowed, clumsy and awkward. Deep tendon reflexes on the affected side were either decreased, normal or exaggerated, and were unrelated to the above mentioned motor deficits. The same held true for deficits of sensation. Demographic, aetiopathological and clinical details of the 16 patients are given in Table 1.

Beyond these ‘common’ clinical findings in the stroke patients mentioned above, our 16 patients shared some specific motor deficits. When the power of individual muscles or muscle groups was tested by an isometric force pulse paradigm, either by means of strain gauges or clinically, it became obvious that the patients had difficulties in initiating activity of the target muscles at will. When the patients were asked to perform the isometric ramp force task, they were unable to start the isometric contraction, although they reported continuous effort. Only on specific verbal enforcement, could the patients eventually initiate the task. Furthermore, patients were not able to maintain a stable tonic isometric contraction. Although also affected, early peak force was relatively less decreased when compared with the level of subsequent tonic activation within the isometric force pulse task. The phenomenon was present in proximal and distal muscles of both the upper and the lower extremities. This motor behaviour was studied semiquantitatively in four patients. In Fig. 1 examples of the characteristic features of the motor deficit are demonstrated. Figure 1A shows surface EMG recordings of the affected (upper trace) and intact (lower trace) FDI obtained 5 weeks post-stroke in patient S.D. When asked to abduct the index finger isometrically against a firm resistance (strongly and radially), on the affected side, recordings show periods of abruptly occurring pauses and rebounds in EMG activity, whereas on the intact side the patient is able to maintain relatively stable tonic activity. Visual feedback of EMG of force was not used.

to the conditioned response. Values of $P < 0.05$ were considered to indicate significance. If not stated otherwise results represent means and SDs of responses to 10 stimuli.

**Results**

Of the 174 patients initially examined, 16 met the criteria for inclusion in the study: Acute central hemiparesis and markedly prolonged SP duration (2 times the intact side) in the affected FDI in the presence of normal MEP amplitudes and latencies. Thus, the frequency of this cliniconeurophysiological symptomatology amounted to ~10%.

**The acute cliniconeurophysiological syndrome**

Although the group of patients was primarily defined neurophysiologically by TMS a striking similarity of clinical presentations was noted. A retrospective analysis of those 158 patients who did not meet the criteria for inclusion revealed a lack of the syndrome outlined below.

**Clinical findings**

Initially all 16 patients had substantial motor deficits; 10 patients presented with a hemiparesis of brachiofacial
Table 1 Clinical details and results of the first SP measurements of the 16 patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Side</th>
<th>Pathology</th>
<th>Clinical findings (excluding features of neglect)</th>
<th>Hemineglect findings</th>
<th>Mean SP (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.A.</td>
<td>67</td>
<td>M</td>
<td>L</td>
<td>Cardiogenic embolic MCA-infarction</td>
<td>R hemiplegia, slight increase of R TR, PR down, R tactile hemihypaesthesia, sensorimotor aphasia, ideatory apraxia</td>
<td>Motor neglect</td>
<td>1670</td>
</tr>
<tr>
<td>G.B.</td>
<td>59</td>
<td>M</td>
<td>R</td>
<td>Cardiogenic embolic MCA-infarction</td>
<td>Conjugate deviation, moderate L brachiofacial hemiparesis, increase of L TR, PR down</td>
<td>Tactile and motor neglect, HSOD</td>
<td>910</td>
</tr>
<tr>
<td>A.B.</td>
<td>75</td>
<td>F</td>
<td>R</td>
<td>MCA-infarction, cause undetermined</td>
<td>L hemiplegia, increase of L TR, L PR up</td>
<td>Tactile and motor neglect</td>
<td>671</td>
</tr>
<tr>
<td>H.B.</td>
<td>78</td>
<td>M</td>
<td>L</td>
<td>MCA-infarction from aortic arc embolism</td>
<td>Severe L brachiofacial hemiparesis, slight increase of L TR, PR down, slight hemihypalgia</td>
<td>Motor neglect</td>
<td>810</td>
</tr>
<tr>
<td>K.B.</td>
<td>72</td>
<td>M</td>
<td>R</td>
<td>MCA-infarction from emboligenic ICA stenosis</td>
<td>Incomplete L hemianopia, moderate L hemiparesis, ataxia of finger-to-nose testing, no reflex abnormalities, PR down</td>
<td>Tactile and motor neglect</td>
<td>636</td>
</tr>
<tr>
<td>S.D.</td>
<td>58</td>
<td>F</td>
<td>R</td>
<td>Cardiogenic embolic MCA-infarction</td>
<td>Conjugate deviation, L hemiplegia, no reflex abnormalities, PR down, anosognosia</td>
<td>Visual, tactile and motor neglect, HSOD</td>
<td>2358</td>
</tr>
<tr>
<td>A.E.</td>
<td>57</td>
<td>M</td>
<td>L</td>
<td>Hypertensive basal ganglia haemorrhage</td>
<td>Moderate parexis R distal upper extremity, R decreased TR, PR equivocal, hypepesthesia R hand</td>
<td>Motor neglect</td>
<td>593</td>
</tr>
<tr>
<td>E.G.</td>
<td>39</td>
<td>F</td>
<td>L</td>
<td>Post-infectious cerebral vasculitis</td>
<td>Moderate R brachiofacial hemiparesis, increased R TR, no R PR, sensory aphasia</td>
<td>Visual, tactile and motor neglect</td>
<td>1186</td>
</tr>
<tr>
<td>B.K.</td>
<td>41</td>
<td>M</td>
<td>L</td>
<td>MCA-infarction from intracranial occlusive artery disease</td>
<td>Moderate R brachiofacial hemiparesis, no reflex abnormalities, R PR up, sensorimotor aphasia</td>
<td>Motor neglect</td>
<td>1098</td>
</tr>
<tr>
<td>R.L.</td>
<td>65</td>
<td>F</td>
<td>R</td>
<td>MCA-infarction from ICA-occlusion</td>
<td>Moderate L hemiparesis, increase of L TR, PR down, L tactile hemihypaesthesia</td>
<td>Tactile and motor neglect</td>
<td>597</td>
</tr>
<tr>
<td>P.L.</td>
<td>59</td>
<td>M</td>
<td>L</td>
<td>MCA-infarction from emboligenic ICA stenosis</td>
<td>R hemiplegia, no reflex abnormalities, PR down, motor aphasia</td>
<td>Motor neglect</td>
<td>483</td>
</tr>
<tr>
<td>E.L.</td>
<td>83</td>
<td>F</td>
<td>R</td>
<td>Cardiogenic embolic MCA-infarction</td>
<td>Conjugate deviation, L hemiplegia, increased L TR, L PR up</td>
<td>Tactile and motor neglect, HSOD</td>
<td>624</td>
</tr>
<tr>
<td>R.S.</td>
<td>54</td>
<td>F</td>
<td>R</td>
<td>MCA-infarction from ICA-occlusion</td>
<td>L hemiplegia, increased L TR, L PR up</td>
<td>Tactile and motor neglect</td>
<td>436</td>
</tr>
<tr>
<td>S.V.</td>
<td>49</td>
<td>F</td>
<td>R</td>
<td>Cardiogenic embolic MCA-infarction</td>
<td>Conjugate deviation, severe L hemiparesis, no reflex abnormalities, L PR equivocal, anosognosia</td>
<td>Visual, tactile and motor neglect, HSOD</td>
<td>747</td>
</tr>
<tr>
<td>A.W.</td>
<td>78</td>
<td>F</td>
<td>L</td>
<td>MCA-infarction from emboligenic ICA stenosis</td>
<td>R moderate hemiparesis, no reflex abnormalities, PR down</td>
<td>Visual, tactile and motor neglect, HSOD</td>
<td>531</td>
</tr>
<tr>
<td>H.Z.</td>
<td>62</td>
<td>M</td>
<td>L</td>
<td>MCA-infarction from ICA-occlusion</td>
<td>R hemiplegia, slight increase of R TR, R PR up, motor aphasia, anosognosia</td>
<td>Tactile and motor neglect</td>
<td>501</td>
</tr>
</tbody>
</table>

The SP duration in the initially hemiplegic patients was evaluated after they had regained the ability to contract their FDI muscle (2–14 days after admission). MCA = middle cerebral artery; ICA = internal carotid artery; TR = deep tendon reflexes; PR = plantar response; up = upgoing; down = downgoing. HSOD = hemispatial orientation deficit.

could not produce a constant level of activation in either of the two tasks. These sudden involuntary pauses in EMG activity were present in all four of the patients who were systematically dynamometrically investigated.

Whereas some of the above-mentioned features of the syndrome closely resembled the description of pure motor neglect given in the classical papers of Watson et al. (1978) and Laplane and Degos (1983), other behavioural manifestations of hemineglect were also noted in a high proportion of the 16 patients (see also Table 1). Heminattention, extinction to simultaneous stimuli (e.g. visual and tactile) and hemispatial orientation deficits were also present to various degrees and in various combinations, as behavioural manifestations of neglect. At least one of these features of hemineglect was noted in 12 of the 16 patients. In four of the 12 patients with features of hemineglect the lesion was located on the left side. In addition, in three patients anosognosia was present during the first 2 weeks.
Fig. 2 Force production with visual feedback. Results from patient S.D., 5 weeks post-stroke. Force signals are shown in the lower part, EMG signals in the upper part of each of the four panels. The patient was asked to abduct her index finger against a strain gauge mounted firmly on the table and to produce maximal isometric force (right panels) or 10% of maximal isometric force (left panels) with the affected as well as with the intact side. These tasks were accomplished perfectly well with the intact side. By contrast, on the affected side reduction of maximal isometric force is demonstrated. Furthermore, the patient was unable to produce a constant level of force. Lapses in force production of the affected hand are accompanied by intermittent breaks in EMG activity.

Lesion analysis disclosed that in all patients the precentral gyrus and the pyramidal tract were spared, with the possible exception of patient S.V., in whom the posterior limb of the internal capsule was affected. In Fig. 3 lesions are depicted schematically in relation to templates derived from the atlas of Matsui and Hirano (1978). In the majority of the patients the lesion was located subcortically. No predominant lesion site could be detected. Of the 16 patients eight had lesions of the left and eight of the right hemisphere.

Findings on magnetic brain stimulation
In the 10 patients without hemiplegia presentation, the typical electrophysiological phenomenon of SP prolongation was present at the first TMS examination within the first 2 weeks post-stroke. In the six initially-plegic patients the extreme prolongation of the SP (mean >2 times mean of intact side) could be detected after they had regained the ability to contract the affected FDI sufficiently to enable SP measurements. In two patients this happened as early as on the second day post-stroke, in the other patients within 14 days. Four of the six patients with initial complete hemiplegia had been examined with TMS when they were still unable to produce preactivation of the target muscle. In all four of these patients, MEPs could be recorded from the FDI of both the affected and the unaffected side; however, these MEPs were significantly reduced in amplitude or prolonged in latency, or both.

Evaluation of conventional TMS parameters in all 16 patients revealed that central motor latencies to the FDI were virtually equal on both sides (affected side, 6.6 ± 0.7 ms; unaffected side, 6.6 ± 0.9 ms; no significant difference). All individual relative amplitudes recorded in our patient group, both of the unaffected and affected side, were within normal limits as determined in a group of normal subjects (Kloten et al., 1992). However, the group mean of relative MEP amplitudes was slightly smaller on the affected side (40 ± 14% of maximal M-response) compared with the intact side (58 ± 20%; P < 0.01). In the individual patient, the reverse could be true, indicating that prolongation of the SP on the affected side was not dependent on a decrease of relative MEP amplitudes. Although normal stimulation thresholds were not part of the inclusion criteria, there was no significant difference between affected and non-affected hemispheres (affected side, 50 ± 10% of maximal stimulator output; intact side, 48 ± 9%; n.s.). Furthermore, there was no hint of a dissociated lowered threshold of the SP in the affected hemisphere; when stimulation was increased stepwise, in no case did an SP occur earlier than a MEP.

Figure 4A illustrates gross acute SP prolongation in the affected FDI as compared with the intact FDI (Patient S.D.). Clinically, the patient had a mild hemiparesis at the time of neurophysiological examination and was unable to perform fractional movements with her left fingers. In addition, hemineglect of the left side of the body was present. When TMS was performed, the patient had to be given additional encouragement, not only to preactivate the target muscle on
Motor abnormalities and exaggerated cortical inhibition

Fig. 4 Abnormally prolonged silent periods, all recorded in Patient S.D., 21 days post-stroke. (A) Three consecutive trials of original EMG recordings of the affected (left) and intact (right) FDI. End of the SP is indicated by arrows. The mean SP (10 trials) was 1051 ms (±412 ms) on the affected side and 210 ms (±7 ms) on the intact side. (B) Demonstration of prolonged inhibition in a conditioning–test stimulus paradigm (interstimulus interval 500 ms). Five pairs of stimuli were delivered through the same stimulation coil with the target muscle at rest; the conditioning stimulus was 1.5 times threshold and the test stimulus 1.2 or 1.5 times threshold. The MEP response is expressed as a percentage of the amplitude following the conditioning stimulus (for test stimulus intensity 1.5 times threshold) or from unconditioned trials using 1.2 times threshold intensity (for test stimulus intensity 1.2 times threshold).

Fig. 3 Sites of the lesions in patients with an abnormally prolonged silent period. Lesions are depicted schematically relative to templates derived from the atlas of Matsui and Hirano (1978). Axial slices with the largest extension of the lesion were selected. Left in the templates corresponds to right in the patient. Note that the primary motor cortex is not affected.

the affected side, but to maintain a constant tonic activation during repeated magnetic stimulation.

In parallel with the prolongation of the SP, a prolonged inhibition of the MEP was also observed in a double stimulation paradigm (Inghilleri et al., 1993; Roick et al., 1993) in two patients. In this paradigm, a MEP in the target muscle is elicited at rest by a conditioning cortical stimulation of 1.5 times motor threshold which is followed by a second test stimulus of either 1.2 times or 1.5 times motor threshold at various intervals. The results are illustrated in Fig. 4B. With a stimulation strength of 1.2 times threshold and an interstimulus interval of 500 ms, the test response was fully suppressed on the affected side, whereas there was no significant inhibition on the intact side. With a stronger test stimulus of 1.5× motor threshold, suppression of the test response was still significant although less pronounced. Even at an interstimulus interval of 1000 ms (not illustrated) there was a significant decrease of the test response on the affected side of 64% when the unconditioned test response was set to 100% (P < 0.05). Similar results were obtained in another patient with a mean SP of 607 ms on the affected side. Such an inhibition was present at an interstimulus interval of 500 ms but not of 1000 ms.

In four patients (S.D., R.S., S.V. and A.W.) the following observations were made. When the initial complete plegia had subsided so that preactivation of the target muscle was possible to some degree, TMS was followed by a virtual inability to activate the target muscle voluntarily in a number of trials, despite the fact that the patients reported a continuous effort. This ‘induced neglect/plegia’ lasted for ≥10s, and it was not included in the calculation of the SP durations. In these instances, additional and continuous encouragement by the investigator was required to persuade the patient to resume voluntary activation of the target muscle.

In our cohort of 174 patients, severe neglect phenomena, including motor neglect, were always associated with a markedly prolonged SPs.
**Clinical improvement accompanied changes in SP duration**

Ten of the 16 patients were assessed for >3 months post-stroke and clearly improved when the motor deficit in the acute stage (first 2 weeks) was compared with the chronic stage (3 months post-stroke and longer). Six initially plegic patients improved within 2–14 days post-stroke and subsequently developed the above defined clinico-neurophysiological syndrome. When motor function began to improve, the symptoms of the syndrome changed in a stereotyped pattern. The ability to initiate isometric finger movements voluntarily recovered first, followed by peak force. Thereafter, the presence of stimulation-induced neglect/plegia disappeared, performance of individual finger movements became possible and under-utilization of the affected limb subsided. In the majority of patients (n = 8) mild motor deficits (problems in holding a constant force level, in precise scaling of various submaximal tonic force levels and slowing of alternating or tapping finger movements) with little functional impairment persisted into the chronic stage.

Clinical improvement was accompanied by a shortening of the SP over time. This finding is demonstrated for patient H.B. in Fig. 5 where representative recordings of the SP during clinical recovery are shown. TMS was performed in this patient at day 6 (Fig. 5A), day 11 (Fig. 5B) and after a year (Fig. 5C). On day 6, the SP in the affected FDI was markedly prolonged and variable (810 ± 286 ms), whereas the SP of the unaffected side was within the normal range (233 ± 6 ms) (dashed lines). Clinically, the patient presented with a severe hemiparesis with reduced force production, difficulties in initiation of voluntary movements and under-utilization of the affected side. On day 11, the SP was less variable, but still markedly prolonged (affected side, 506 ± 22 ms; unaffected side, 225 ± 15 ms). At this time under-utilization had improved but peak force production was still reduced and initiation of voluntary movement was still impaired. After a year, values of the SP returned to an almost normal level on the affected side (309 ± 25 ms; unaffected side, 209 ± 13 ms), clinically the patient showed only some residual slowing of alternating finger movements.

In two patients (G.B. and E.G.) an intermittent clinical deterioration within the first 2 weeks was accompanied by a further increase of SP durations on the affected side which (similar to the other patients) subsided with later clinical improvement.

The finding of severely prolonged SP durations accompanying the above described clinico-neurophysiological syndrome and renormalization of the SP duration in parallel with clinical improvement was not restricted to patients with ischaemic or haemorrhagic lesions of the brain. The same phenomena were observed in a case with a cerebral lymphoma located in the right temporo-parietal region. In this case, a shortening of the SP duration of the affected side from a mean of 967 ms to a mean of 365 ms was observed within 4 weeks of starting treatment with adriamycin, vincristin, cyclophosphamide and prednisolone, which reduced the volume of the tumor considerably. Concomitantly, motor functions had improved markedly at the time of the second examination.
Motor abnormalities and exaggerated cortical inhibition

Fig. 6 Comparison of the SP durations in the acute (first 2 weeks) and chronic (90 days and more) stages. Results from the 10 patients in whom TMS investigations could be performed in the chronic stage. Individual results (two inner positions) as well as group means (two outer positions) are given for the acute and chronic stages on the affected and intact side. Mean duration of the SP on the affected side was markedly prolonged in the acute stage reflecting the inclusion criterion. In the chronic stage the SP duration on the affected side had shortened to a near normal range.

In Fig. 6 measurements in the 10 patients who were examined in both the acute and chronic stage are summarized. In the acute stage the mean duration of the SP on the affected side was 922 ± 563 ms and that on the intact side was 233 ± 28 ms. However, in the chronic stage the mean duration of the SP on the affected side was almost normal (253 ± 81 ms) when compared with the unaffected FDI (202 ± 40 ms). The difference between affected and intact sides was significant in the acute stage (P < 0.01) and in the chronic stage (P < 0.05). On the affected side there was a significant difference between the acute and the chronic stage (P < 0.01), whereas on the intact side, the difference between acute and chronic stage was not significant. Within the patient group a clearly abnormally prolonged SP could be detected in only two cases in the chronic stage (461 and 309 ms). Apart from that in one patient (P.L.), who showed normalization of the SP duration as early as 14 days post-stroke, the SP remained prolonged in the acute stage. Investigations which were performed in the intermediate stage, 2 weeks to 3 months post-stroke, revealed a progressive shortening of the SP duration, with normalization completed at ~6–12 weeks in the majority of patients (eight out of 10). Also in the six patients who could not be followed into the chronic stage (>3 months) a decline of the SP duration of the affected side had already been observed with successive measurements within the first 3 months post-stroke.

MEP thresholds, amplitudes and latencies are summarized in Table 2 for the 10 patients who were studied in both the acute and chronic stages. When the affected and intact sides were compared, the mean value of central motor latencies of the intact side was found to be slightly shortened (by <1 ms) in the chronic stage (P < 0.05). MEP amplitudes on the affected side were relatively reduced in the acute stage (P < 0.01), as was mentioned above for the whole group of 16 patients. However, in the chronic stage there was no longer a significant difference between the two sides. Furthermore, comparison of acute and chronic stages using any of these parameters obtained from the affected side did not reveal any significant differences.

SP durations of patients were compared not only with those from the side ipsilateral to the lesion, but also with values obtained from 16 normal age- and sex-matched control subjects. The mean SP duration in the control group was 181 ± 12 ms on the left and 180 ± 10 ms on the right side (range 166–228) ms and thus similar to values reported before (Roick et al., 1993) when adjusted for the difference in their definition of SP duration. As required by the inclusion criteria, the SP duration of the affected side in patients was highly significantly prolonged compared with that of the control subjects (P < 0.001). When the ‘unaffected’ side was compared with normal values a significant prolongation was noted in the acute stage (P < 0.01). This difference was no longer significant in the last SP measurement in the 10 patients in whom SPs could be measured in the chronic stage.

Discussion

It was the aim of the present study to assess the motor deficits in patients with unilateral lesions of the cerebral hemispheres who showed an abnormally prolonged SP. The primary motor cortex was not structurally affected by the lesions, and MEPs were normal in these patients. Our initial hypothesis was that exaggerated inhibitory activity within the motor cortex, as reflected by an increased SP, is associated with distinct patterns of motor abnormalities.

Of 174 consecutive patients entering the hospital with
acute stroke, 16 fulfilled the above-mentioned selection criteria for enrollment into the study. Although the severity of the motor deficit and the extent and site of the cortical and subcortical lesions varied among the patients, a stereotyped clinical syndrome could be detected. The main features of this syndrome were muscular weakness, disturbance of isolated finger movements, absence or paucity of spontaneous movements, impairment of movement initiation, slowness of movements, and problems in scaling submaximal force levels and in holding a constant force. In addition, TMS intermittently induced inability to activate the target muscle. Most of these symptoms have traditionally been described as components of motor neglect and have, in this context, been termed akinesia, bradykinesia, hypometria and motor impersistence (e.g. Simon et al., 1995). The presence of further symptoms of hemineglect such as semi-inattention, extinction to simultaneous stimuli and hemispatial orientation deficits is frequently associated with motor neglect and was observed in three-quarters of the patients.

Clinical improvement in our patients was paralleled by a decrease of the contralesional SP duration, and in the majority of patients this occurred within ~7 weeks. We put forward the hypothesis that SP prolongation may play a crucial pathophysiological role in this motor syndrome.

**Mechanisms of SP prolongation**

The SP can be observed when the contralateral primary motor cortex is magnetically stimulated, during tonic activation of the target muscle. At a constant stimulation strength (e.g. 1.5 times resting threshold) the SP is most pronounced in small hand muscles such as the FDI and lasts for ~150–240 ms (Inghilleri, et al., 1993; Roick et al., 1993). A number of groups (Fuhr et al., 1991; Cantello et al. 1992; Inghilleri et al., 1993; Roick et al., 1993) have investigated the SP with respect to its spinal or cortical origin and have come to the conclusion that it is mainly generated cortically, especially in its later part. Some of the experiments on the physiology of the SP have employed double magnetic stimulation of the relaxed muscle (Claus et al., 1992; Valls-Solé et al., 1992; Roick et al., 1993). It turned out that the MEP response to the second of two stimuli could be reduced in amplitude for a period similar in length to the SP seen after single TMS (Claus et al., 1992; Valls-Solé et al., 1992; Roick et al., 1993; Berardelli et al., 1996). It seems possible that similar mechanisms are operative for the SP observed in the active muscle and for the suppression of the second response in the paired stimulus paradigm in the resting muscle. Berardelli et al. (1996) have recently observed a dissociation of the SP duration and paired pulse inhibition in Parkinson’s disease patients, and have concluded that the interneuronal subsets generating the two phenomena are different. In the two of our patients whom we could study using the paired pulse paradigm (see also Fig. 4) the second pulse was suppressed when applied at an interval shorter than the SP duration, but it was not significantly changed when applied at a longer interval. This finding indicates the presence of exaggerated inhibition in the motor cortex in these patients as opposed to a lack of voluntary drive directed to the motor cortex and, following the reasoning of Berardelli et al. (1996), suggests that the control of both subsets of interneurons was affected.

Also in single motor units, voluntarily activated firing is suppressed following the short latency excitation evoked by magnetic stimulation. Recently Classen and Benecke (1995) have shown that, in motor units recruited at low force levels, the length of the SP can exceed that observed in the surface EMG (determined by the motor units with the shortest SP) by several hundred milliseconds if the intensity of the magnetic stimulus is slightly higher than threshold intensity for the short latency response. It has been suggested (Classen and Benecke, 1995) that the long SP in single motor unit recordings at just suprathreshold magnetic stimulation may be caused by an activation of cortical GABAergic inhibitory interneurons which are, in this situation, under less mutual inhibitory control. GABAergic interneurons may be excited by axon collaterals of a small subset of pyramidal output cells or by afferents impinging on the GABAergic interneurons (see also Mc Cormick, 1992). Excitation of local GABAergic inhibitory interneurons elicited by electrical stimulation of afferent fibres was followed by biphasic inhibitory postsynaptic potentials lasting several hundred milliseconds in cortical output cells of human neocortex slices (Mc Cormick, 1992). Activation of postsynaptic GABA_A receptors resulted in a short lasting inhibitory postsynaptic potential (in the order of tens of milliseconds) in pyramidal cells, whereas a long lasting inhibitory postsynaptic potential (in the order of hundreds of milliseconds) was generated by activation of GABA_B receptors (Mc Cormick, 1992). Correspondingly, it could be assumed that TMS induced SPs in the order of 100–300 ms are mediated mainly by activation

<table>
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<th>Threshold (% max output)</th>
<th>Central motor latency (ms)</th>
<th>Relative MEP amplitudes (%)</th>
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<tr>
<td></td>
<td>Affected side</td>
<td>Intact side</td>
<td>Affected side</td>
</tr>
<tr>
<td>Acute</td>
<td>48 ± 7</td>
<td>47 ± 9</td>
<td>6.7 ± 0.8</td>
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<tr>
<td>Chronic</td>
<td>42 ± 6</td>
<td>43 ± 8</td>
<td>6.7 ± 1.0*</td>
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Significant differences were found between intact and affected sides in the acute stage for relative MEP amplitudes (**P < 0.01) and in the chronic stage for central motor latencies (*P < 0.05). There were no other significant differences between the affected and intact sides, and no significant differences between parameters comparing the acute and chronic stages.

Table 2 Comparison of TMS parameters in the acute and chronic stage post-strike
of GABAB receptors, whereas long SPs lasting several hundred milliseconds are caused by substantial GABA_B receptor activation (Classen and Benecke, 1995). Alternatively, extremely long SPs could also result from sustained firing of inhibitory interneurons.

Theoretically, the abnormally prolonged SPs in the patients of the present study may be caused by a defect in mutual inhibition between the GABAergic interneurons, by a pathologically enhanced excitatory input to these interneurons, or by a decrease of inhibitory control on them. Since the inhibitory action of the GABAergic interneurons is well preserved at the PT cells, as reflected by the prolonged SP duration, it is unlikely that it is selectively abnormally low in collaterals impinging on the neighboring inhibitory interneurons (mutual inhibition). We favour the idea that, in our patients, the various lesions which spared the primary motor cortex and the pyramidal tract mainly result in a de-afferentation of the primary motor cortex. Loss of afferent, e.g. thalamo-cortical, striato-cortical and cortico-cortical nerve fibres towards the motor cortex, may decrease the excitatory input not only on pyramidal cells but also on intracortical inhibitory interneurons. Overactivity of the GABAergic inhibitory interneurons which mediate the SP phenomenon may result from decreased inhibitory influence from those inhibitory interneurons which are directly activated by afferent systems (disinhibition). Loss of afferent control might result in failure to terminate stimulus-induced activity of the GABAergic interneurons which activate GABA_B receptors, and subsequently induce a prolonged inhibition of pyramidal output cells. Such an abnormally powerful inhibitory action of PT cells may also be present during tonic and phasic activation of PT cells in natural motor actions and substantially affect the output activity.

Although the stimulus intensity for assessment of the SP duration was higher in the acute than in the chronic stage as a consequence of slightly (but insignificantly) higher motor thresholds (Table 2) this difference is unlikely to account for the pathologically enhanced SP duration also observed in the ‘intact’ body side in the acute stage. Schnitzler et al. (1996) have shown that, in normal subjects, the SP is shortened by ipsilateral conditioning with magnetic stimulation, suggesting that inhibition in one hemisphere may be under control from the other hemisphere (see also Meyer et al., 1995). It seems possible that a reduced excitatory input from the damaged hemisphere may result in a net overactivity of inhibitory interneurons also in the intact side and may contribute to ipsilateral weakness after stroke (Colebatch et al., 1989).

**Motor disturbances caused by abnormal intracortical inhibition**

It is generally believed that the functional role of inhibitory interneurons is to focus activity by means of lateral inhibition, to stabilize and limit output frequencies by recurrent inhibition and to enable gain control. Both a diminished and an exaggerated activity of such an inhibitory interneuronal system can result in abnormalities of the neuronal circuitry.

One example of a motor disturbance caused by exaggerated inhibition is negative cortical myoclonus which is characterized by brief lapses of tonic voluntary activity occurring either spontaneously or as a response to peripheral electrical nerve stimulation. Shibasaki et al. (1994) provided evidence that the stimulus-sensitive negative myoclonus is mediated by a transcortical reflex mechanism and that exaggerated intracortical inhibitory mechanisms can be triggered by somesthetic input.

Todd’s paresis (post-epileptic paralysis) may represent another example of exaggerated cortical inhibition. Detailed neurophysiological studies, however, have not yet been performed in patients presenting with this type of motor failure.

Decreased intracortical inhibitory activity can also be associated with motor abnormalities. Tonic and clonic motor activities during seizures have been interpreted in terms of defective inhibitory GABAergic mechanisms in animal models of epilepsy (Matsumoto and Ajmone-Marsan, 1964a, b; Ben Ari et al., 1981; Luhmann et al., 1994). In line with these observations are recent findings of a decrease of the SP duration in patients suffering from simple focal motor seizures after stroke (Schnitzler et al., 1994) or epilepsy partialis continua (Classen et al., 1995b).

**The clinical syndrome**

The clinical syndrome in our 16 patients, who had been selected on neurophysiological criteria rather than on their clinical features, was characterized by muscular weakness, disturbance of fractionated finger movements, absence or paucity of spontaneous movements, impairment of movement initiation, slowness of movements, problems in scaling submaximal force levels and in holding a constant force, and by intermittent TMS induced inability to activate the target muscle. Extinction to simultaneous stimuli and hemispatial orientation deficits were present in addition to the above-mentioned motor syndrome. This clinical symptomatology carries a remarkable similarity to the syndrome of motor neglect.

Motor neglect has been defined as an under-utilization of limbs, without defects of muscle strength, reflexes or sensation (Laplane and Degos, 1983). The original criteria introduced by Castaigne et al. (1970, 1972) also put particular emphasis on a number of exclusion criteria such as absence of paresis, absence of muscle tone changes, absence of pyramidal signs, absence of sensation deficits and absence of disturbance of rapid alternating limb movements. These classical definitions of motor neglect have either implicitly or explicitly incorporated the assumption that no motor disorder other than the motivationally responsive is present in such patients. Consequently, on the basis of the Castaigne-criteria (Castaigne et al., 1970, 1972) the clinical syndrome in our patients could hardly be classified as motor neglect.
since paresis and other problems in the performance of limb movements were present. However, in recent years an increasing number of investigators have recognized that patients with under-utilization of one body side indeed also show a number of disturbances in movement performance with problems in movement dynamics and kinematics such as a complete inability to perform a movement (akinesia), a delay in initiating a movement (hypokinesia), a decreased amplitude of movement (hypometria) or an inability to maintain a steady force level (motor impersistence) (Valenstein and Heilman, 1981; Meador et al., 1986; Mattingley et al., 1992; Simon et al., 1995).

It is generally assumed that patients with loss of dexterity and reduced muscle power have PT involvement. Although all individual MEP measurements in the present study were within normal limits, group means of the affected side were reduced when compared with the intact side and some patients showed clinical signs such as upgoing plantar responses and/or increased tendon reflexes suggestive of possible PT tract involvement. In some patients, however, with a similar clinical symptomatology, there was no evidence of PT involvement. In those cases, it seems a conceptual oversimplification to attribute remaining deficits in muscle power to either incomplete motivation or minor damage of the pyramidal tract. Often, in clinical practice, the only statement that can be made with certainty is that the muscle power is, on additional motivation, greater than that observable during studies of motor cortical output, as in the analysis of thalamic tract pathways. As to the underlying pathophysiological mechanism, motor neglect could be the result of a disturbance of a complex network (Heilman et al., 1992). So far, however, neither neuroanatomical nor physiological studies support the idea of a highly complex motor network which incorporates all the cerebral areas (motor cortices, basal ganglia, thalamus, parietal and prefrontal cortical areas) in which lesions can be associated with motor neglect. In contrast, in studies of motor cortical output, as in the analysis of thalamic innervation, an important concept has evolved in which descending corticostratial pathways are organized in parallel loops rather than as convergent projections (Alexander et al., 1986). It is suggested that each of these separated loops has its own functional role, and lesions of these loops lead to distinct motor disturbances.

Pathophysiological significance of silent period prolongation

A number of arguments point towards a crucial pathophysiological role of exaggerated intracortical inhibition, as reflected by the increased SP duration, for the genesis of motor neglect. First, the close relationship between a prolonged SP and the presence of the syndrome. SP normalization is associated with clinical improvement and clinical deterioration is accompanied by an increase in the SP duration (Patients G.B. and E.G.). Secondly, in some patients TMS intermittently induced a motor behaviour resembling motor neglect accompanied by a grossly prolonged electrical silence in the target muscle. Thirdly, the stereotyped co-occurrence of both an exaggerated SP duration and motor neglect is remarkable in view of the wide spectrum of lesions affecting various sensorimotor systems in our patients.

In contrast to other motor syndromes (e.g. upper motor neuron syndrome, parkinsonian syndrome, chorea), and corroborated in our study, motor neglect has been reported to occur with lesions in anatomically quite distinct brain areas (Castaing et al. 1972; Watson et al., 1973, 1974, 1978; Watson and Heilman 1979; Damasio et al., 1980; Heilman et al., 1983). As is demonstrated in Fig. 3 the lesions involved the thalamus, parietal and premotor cortices or subcortical pathways. As to the underlying pathophysiological mechanism, motor neglect could be the result of a disturbance of a complex network (Heilman et al., 1992). So far, however, neither neuroanatomical nor physiological studies support the idea of a highly complex motor network which incorporates all the cerebral areas (motor cortices, basal ganglia, thalamus, parietal and prefrontal cortical areas) in which lesions can be associated with motor neglect. In contrast, in studies of motor cortical output, as in the analysis of thalamic innervation, an important concept has evolved in which descending corticostratial pathways are organized in parallel loops rather than as convergent projections (Alexander et al., 1986). It is suggested that each of these separated loops has its own functional role, and lesions of these loops lead to distinct motor disturbances.

On the basis of our findings, we favour the idea that motor neglect is a stereotyped motor disturbance, which occurs whenever there is overactivity of inhibitory interneurons within the motor cortex which disturbs the output activity of PT cells. Various lesions of cortical and subcortical areas which are directly or indirectly connected to the primary motor cortex (Jones, 1986) may lead to deafferentation and result in an imbalance of interneuronal intracortical activity which favours inhibitory interneurons. When motor neglect is severe, specific motor disturbances due to loss of specific projecting systems may be masked. On the other hand, motor neglect may be masked when the output system itself (primary motor cortex, pyramidal tract) is damaged. The mechanism responsible for the often rapid (days or weeks) SP renormalization and improvement of motor neglect is intriguing and not apparently clear. Plastic changes of GABA receptors and intracortical sprouting of intact afferent fibres are possible candidates.

In Parkinson’s disease a decrease in the SP duration has been observed which could be partially renormalized by L-Dopa administration (Berardelli et al., 1996). In this disease the negative motor symptoms may be induced largely by insufficient facilitatory input to the motor cortex rather than
by exaggerated intracortical inhibition, as was observed in the present study in motor neglect.

It has long been postulated that the various manifestations of neglect are generated by a common neurophysiological mechanism (Laplane, 1990). One may now speculate that deafferentation of various cortical areas leading to excessive inhibition, similar to that demonstrated in the motor cortex by the SP prolongation, produce clinical symptomatologies such as hemispatial orientation deficits, hemiextinction and even disturbances of visuomotor behaviour or other focal deficits. Such deafferentations might have their metabolic correlates in remote metabolic depressions (Metter, 1987; Seitz et al., 1994; von Giesen et al., 1994b), but they cannot be as easily assessed neurophysiologically as those in the motor system.

In summary, we suggest that in a selected subgroup of patients with hemiparetic stroke a number of motor abnormalities, including features of motor neglect, are caused by deafferentation of the primary motor cortex and by hyperactivity of inhibitory interneurons rather than by direct lesion of the corticospinal tract.

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