Motor Cortex Excitability After Cerebellar Infarction

J. Liepert, MD; T. Kucinski, MD; O. Tüscher, MD; F. Pawlas, MD; T. Bäumer, MD; C. Weiller, MD

Background and Purpose—The cerebellum has an influence on motor excitability. We investigated if the location of a cerebellar infarction was crucial for changes of motor cortex excitability and if the electrophysiological findings were correlated with motor performance.

Methods—Transcranial magnetic stimulation was applied to study intracortical inhibition (ICI), intracortical facilitation (ICF), motor thresholds, and corticospinal excitability. Dexterity as a measure of motor performance was tested with the Nine-Hole-Peg Test (9HPT). Ratios (affected/unaffected) were also calculated.

Results—ICI and ICF ratios were negatively correlated with 9HPT ratios in all patients (n = 9). Compared with an age-matched control group, patients with lesions in the territory of the superior cerebellar artery (SCA) (n = 3) or a lesion rostral of the dentate nucleus (n = 1) had abnormally enhanced ICI and a loss of ICF (3 patients). Dexterity was impaired in all 4 patients. Motor excitability and motor performance normalized over the subsequent weeks. Patients with an infarct either in the territory of the anterior inferior cerebellar artery (n = 2) or in the territory of the posterior inferior cerebellar artery (n = 3) displayed motor excitability and motor performance within the normal range.

Conclusion—The superior part of the cerebellum has a strong influence on motor cortex excitability. We suggest that the enhancement of motor inhibition and reduction of motor facilitation is mediated by an impairment of the deep cerebellar nuclei.

Key Words: cerebral infarction • cerebellar disease • electromagnetics • superior cerebral arteries

The cerebellum plays an important role for different aspects of motor performance, e.g., coordination, timing, and dexterity. Animal experiments have indicated that the motor areas receive excitatory input from the cerebellar nuclei, which is important for the generation of voluntary movement.1–4 Ischemic cerebellar infarctions produce distinct clinical patterns including motor disturbances such as limb dysmetria, intention tremor, axial lateropulsion, and dysarthria. Preceding studies with transcranial magnetic stimulation (TMS) have shown that the threshold for the production of motor evoked potentials (MEPs) is elevated in humans with acute unilateral cerebellar lesions.5–8 This finding indicates a reduction of corticospinal excitability but does not specifically address the question if cerebellar infarctions modify motor excitability on a cortical level. Today, a combination of different TMS techniques allows to differentiate modulations of inhibitory and facilitatory properties of the motor system. In this study, we included patients with ischemic infarctions in the territories of the 3 predominant cerebellar arteries to investigate the effects of distinct cerebellar lesions on facilitatory and inhibitory properties of the motor system and to correlate these findings with clinical symptoms. The aim was to determine if changes of motor excitability could be associated with particular anatomical cerebellar areas.

Materials and Methods

We studied 8 patients (4 male; age range, 38 to 81 years) with embolic territorial cerebellar infarctions. The origin was either cardiogenic embolism or emboli associated with dissective occlusion of a vertebral artery (Table 1).

Cases 1 to 3 had infarctions in the territory of the superior cerebellar artery (SCA) (Figure 1A). In case 2, a large SCA infarct had occurred in the left cerebellum and, simultaneously, an additional small infarct was present in the right SCA territory. This patient presented severe ataxia of his left arm and minor ataxia of his right arm. In case 3, the ischemic territorial lesion was incomplete and did not destroy the deep cerebellar nuclei. Cases 4 and 5 had an embolic infarct in the territory of the anterior inferior cerebellar artery (AICA) (Figure 1B). Cases 6 to 8 had ischemic infarctions in the territory of the posterior inferior cerebellar artery (PICA) (Figure 1C). To explore the influence of differences from the deep cerebellar nuclei on motor cortex excitability, we studied an additional patient (case 9) with a small lacunar stroke lesion rostral of the dentate nucleus (Figure 1D). All patients except cases 4 and 6 had an impairment of stance and gait. Cases 1 to 3 and case 9 presented limb ataxia ipsilateral to their affected cerebellum. To further characterize the patients’ deficits, we applied the International Cooperative Ataxia Rating scale9 simultaneously with each electrophysiological investigation. The maximum score of 100 indicates severe ataxia.

None of the patients had evidence of an involvement of the brain stem as tested by clinical examination and magnetic resonance tomography of the brain. Because the patients differed in age, results were compared with data from 3 age-matched healthy control groups. One control group consisted of 10 male subjects (mean age, 36.4 years; range, 26 to 41 years). The second control group

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consisted of 10 male subjects with a mean age of 60.5 years (range, 54 to 67 years). In the third control group, 5 male and 5 female subjects (mean age, 76.3 years, range, 66 to 82 years) were included. All patients were examined within the first 2 weeks after their stroke. In case of abnormal electrophysiological results, the examinations were repeated after 5 to 6 weeks. “Abnormality” was considered to be present if the patient’s TMS results were outside 2.5 standard deviations of the mean value of the corresponding control group. Control group data are presented in Table 2.

Patients and control subjects gave their informed consent before the examinations. The study protocol was approved by the local ethics committee.

Motor excitability was assessed using TMS and peripheral electrical stimulation on both sides. We investigated motor thresholds (MT), MEP latency and central motor conduction time. A paired pulse TMS paradigm was used to test intracortical inhibition (ICI) and intracortical facilitation (ICF). Stimulus response curves (SRC) were obtained by application of single-pulse TMS with intensities of 110%, 120%, 130%, 140%, and 150% of the individual motor threshold. SRC, ICI, and ICF were studied during complete muscle relaxation. The ulnar nerve was stimulated electrically at the wrist with supramaximal intensities to study M responses and F waves. Recordings were taken with surface electrodes (belly-tendon montage) from the first interosseous dorsalis muscle. TMS was performed with a figure-of-eight coil with an outer diameter of 70 mm (The Magstim Co), which was connected to a magnetic stimulator (Magstim 200 HP). To apply paired pulses, the coil was connected to a Bistim device, which triggered 2 magnetic stimulators. The interstimulus intervals (ISI) tested were 2, 3, 10, and 15 ms. The stimulus intensity of the first conditioning shock was 75% of MT at rest; the intensity of the second pulse was adjusted to produce a MEP of ~0.5 mV. The coil was held with the grip pointing posteriorly and perpendicular to the central sulcus. For each ISI, 8 stimuli were applied in a randomized order. Recordings were stored on a Viking IV (Nicolet) and analyzed offline. MEP amplitudes and M responses were measured peak to peak. MT was defined as the stimulus intensity that produced MEPs of 50 to 100 μV in 5 out of 10 trials in the resting muscle. ICI consisted of MEP amplitudes produced by TMS with 2 and 3 ms ISI; for ICF, results from ISI of 10 and 15 ms were combined. The values were expressed as percentage of the mean MEP amplitude after single-pulse TMS. The central motor conduction time was calculated by subtracting the peripheral motor conduction time from the latency obtained after TMS. Maximum MEP amplitude obtained with a stimulus intensity 50% above MT during pre-innervation of the target muscle was expressed as percentage of the M response amplitude.

Motor performance was tested using the Nine-Hole-Peg Test (9HPT). The task consists of putting 9 pegs into 9 holes and then removing them as fast as possible. Patients and controls were trained to perform the procedure once and then had to complete the test 2 times. For each trial, the time was clocked in seconds, and a mean of the 2 trials was calculated.

To investigate a relationship between electrophysiological findings and behavior, the 9HPT results were correlated with intracortical excitability results. We calculated ratios (results obtained in the affected side/results from the unaffected side) and correlated ICF and ICI with 9HPT results.

Results

Cases 1 to 3 and 9 presented an abnormally increased ICI for the ataxic hand. ICI normalized during follow-up. In cases 1, 2, and 9, ICF was abnormally decreased and returned to normal values during follow-up. The 9HPT results of the ataxic upper limb were abnormal in all patients (Figures 2 and 3).

Figure 1. Examples of the 3 different types of cerebellar infarcts included in this study. A, Infarct in the territory of the superior cerebellar artery (SCA) (case 1). B, Infarct in the territory of the anterior inferior cerebellar artery (AICA) (case 4). C, Infarct in the territory of the posterior inferior cerebellar artery (PICA) (case 6). D, Lacunar infarct rostral of the right dentate nucleus in a diffusion-weighted magnetic resonance image (case 9).
In cases 4 to 8, all electrophysiological values and the 9HPT results were within the 2.5 standard deviations of the age-matched control groups. However, it is noteworthy that patients 2, 5, and 7 to 9 had higher MTs on the affected side (Table 2). In contrast, patient 6 had a higher MT on the nonaffected side.

In cases 1, 2, 4, and 9, SRC were less steep for the ataxic side. However, none of the values outside the 2.5 standard deviations of the age-matched control groups (Table 2). In contrast, patient 6 had a higher MT on the affected side. The gray square represents the mean value of the affected side; the white squares indicate the unaffected side. The dashed lines show the 2.5-standard deviation (SD) of the mean value of the control group. The black squares represent the mean value of the control group (control 2; mean age, 60.5 years). The black squares represent the mean value of the control group (control 2; mean age, 60.5 years).

**Discussion**

This study suggests that the cerebellar territory supplied by the superior cerebellar artery is the most important cerebellar area for modulation of motor excitability. A large vascular lesion in this territory leads to a loss of ICF and an increase of ICI. The SCA supplies the anterior and rostral parts of the cerebellar hemispheres. These cerebellar cortex areas, particularly the lobules IV–VI, are connected with the primary motor cortex. The deep cerebellar nuclei, particularly the interposed nuclei and the dentate nucleus, are irrigated by deep penetrators from the SCA. Animal studies have revealed that projections from the deep cerebellar nuclei terminate in premotor and motor cortex areas. The dentate nucleus exerts a tonic facilitatory influence on motor cortex and controls multijoint movements. The interpositus controls agonist antagonist synergy and stretch reflexes at a single joint. Thus, it

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**TABLE 2. Electrophysiological Data and Nine-Hole-Peg Test (9HPT) Results in Patients With Cerebellar Infarcts and Control Groups**

<table>
<thead>
<tr>
<th>Case</th>
<th>ICI</th>
<th>ICF</th>
<th>MT</th>
<th>110%</th>
<th>120%</th>
<th>130%</th>
<th>140%</th>
<th>CMCT</th>
<th>max MEP</th>
<th>9HPT</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>UA</td>
<td>A</td>
<td>UA</td>
<td>A</td>
<td>UA</td>
<td>A</td>
<td>UA</td>
<td>A</td>
<td>UA</td>
<td>A</td>
</tr>
<tr>
<td>1, 1ex (C3)</td>
<td>15.5</td>
<td>61.1</td>
<td>10.6</td>
<td>138.1</td>
<td>54</td>
<td>55</td>
<td>2.5</td>
<td>3.8</td>
<td>6.9</td>
<td>9.8</td>
</tr>
<tr>
<td>1, 2ex</td>
<td>58.4</td>
<td>40.5</td>
<td>127.4</td>
<td>118.7</td>
<td>48</td>
<td>51</td>
<td>5.4</td>
<td>5.6</td>
<td>50.6</td>
<td>49.9</td>
</tr>
<tr>
<td>2, 1ex (C3)</td>
<td>7.1</td>
<td>9.2</td>
<td>22.5</td>
<td>82.3</td>
<td>48</td>
<td>44</td>
<td>1.1</td>
<td>1.6</td>
<td>3.5</td>
<td>6.8</td>
</tr>
<tr>
<td>2, 2ex</td>
<td>13.8</td>
<td>18.8</td>
<td>96.2</td>
<td>181.4</td>
<td>47</td>
<td>43</td>
<td>5.7</td>
<td>5.6</td>
<td>65.6</td>
<td>37.6</td>
</tr>
<tr>
<td>2, 3ex</td>
<td>18.7</td>
<td>20.6</td>
<td>184</td>
<td>111.9</td>
<td>46</td>
<td>44</td>
<td>5.7</td>
<td>5.6</td>
<td>62.4</td>
<td>35.7</td>
</tr>
<tr>
<td>3, 1ex (C2)</td>
<td>8</td>
<td>59.4</td>
<td>135.5</td>
<td>214.1</td>
<td>48</td>
<td>48</td>
<td>2.6</td>
<td>1.6</td>
<td>3.4</td>
<td>2.3</td>
</tr>
<tr>
<td>3, 2ex</td>
<td>28.7</td>
<td>64.3</td>
<td>176.3</td>
<td>219</td>
<td>47</td>
<td>47</td>
<td>6.3</td>
<td>5.9</td>
<td>53.7</td>
<td>37.6</td>
</tr>
<tr>
<td>4 (C2)</td>
<td>23.2</td>
<td>22.9</td>
<td>150.3</td>
<td>166.3</td>
<td>49</td>
<td>49</td>
<td>2.2</td>
<td>2.6</td>
<td>10.2</td>
<td>13.4</td>
</tr>
<tr>
<td>5 (C3)</td>
<td>26.9</td>
<td>26.8</td>
<td>188.2</td>
<td>110.3</td>
<td>49</td>
<td>44</td>
<td>2.3</td>
<td>1.5</td>
<td>4.8</td>
<td>6.2</td>
</tr>
<tr>
<td>6 (C1)</td>
<td>58.3</td>
<td>67.9</td>
<td>216.3</td>
<td>185.6</td>
<td>46</td>
<td>57</td>
<td>2.7</td>
<td>1.4</td>
<td>4.6</td>
<td>6.6</td>
</tr>
<tr>
<td>7 (C3)</td>
<td>54.4</td>
<td>34.2</td>
<td>150.9</td>
<td>122.7</td>
<td>58</td>
<td>54</td>
<td>4.9</td>
<td>5.3</td>
<td>44.6</td>
<td>34.1</td>
</tr>
<tr>
<td>8 (C3)</td>
<td>52.1</td>
<td>59.5</td>
<td>118.9</td>
<td>214.6</td>
<td>50</td>
<td>47</td>
<td>1.4</td>
<td>0.9</td>
<td>5.8</td>
<td>4.9</td>
</tr>
<tr>
<td>9 (C2)</td>
<td>16.5</td>
<td>40.4</td>
<td>58.4</td>
<td>138.5</td>
<td>51</td>
<td>46</td>
<td>0.9</td>
<td>1.7</td>
<td>5.9</td>
<td>10.6</td>
</tr>
<tr>
<td>C 1</td>
<td>41 (15-67)</td>
<td>202 (123-281)</td>
<td>45.5 (30-61)</td>
<td>2.2 (0.5-3.9)</td>
<td>5.1 (1.9-8.3)</td>
<td>8.3 (2.3-14.3)</td>
<td>13 (3-23)</td>
<td>17.3 (5.5-31.1)</td>
<td>5.5 (4.1-6.9)</td>
<td>52.7 (25.7-79.7)</td>
</tr>
<tr>
<td>C 2</td>
<td>45.6 (19-71.6)</td>
<td>159 (78-290)</td>
<td>47.2 (24-61)</td>
<td>2.3 (0.6-3.9)</td>
<td>6.9 (2.2-11.6)</td>
<td>11.1 (2.3-19.3)</td>
<td>16.2 (5.8-26.7)</td>
<td>18.8 (9.6-30)</td>
<td>5.7 (4.2-7)</td>
<td>55.7 (24.2-87.2)</td>
</tr>
<tr>
<td>C 3</td>
<td>46.9 (20.6-73.2)</td>
<td>147.5 (76-219)</td>
<td>48.1 (35.4-60.2)</td>
<td>2.6 (1.4-3.8)</td>
<td>5.2 (1.9-8.3)</td>
<td>9.4 (3.9-14.9)</td>
<td>14.1 (6.3-22.8)</td>
<td>18.5 (8.1-28.9)</td>
<td>5.8 (4.3-7.3)</td>
<td>57.2 (28.1-85.3)</td>
</tr>
</tbody>
</table>

Ex indicates examination; A, affected hand; UA, unaffected hand; ICI, intracortical inhibition; ICF, intracortical facilitation; MT, motor threshold; CMCT, central motor conduction time; max MEP, maximum amplitude of the motor evoked potential.

Numbers in bold and italic letters indicate values outside the 2.5-standard deviation of the mean of the age-matched control group. C1 indicates control group with mean age of 36.4 years; C2, control group with mean age of 60.5 years; C3, control group with mean age of 76.3 years. The 2.5-standard deviation interval around the mean value is given in brackets. After each case number, the corresponding age-matched control group is indicated.

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The correlation analysis of motor performance and intracortical excitability revealed a highly significant inverse correlation between the amount of ICF and the ability to perform the 9HPT (Pearson coefficient: $r = -0.933$; $P = 0.00024$; Figure 4B). The correlation between ICI and 9HPT was also significant (Pearson coefficient: $r = -0.717$; $P = 0.029$; Figure 4A).
can be predicted that a loss of these projections leads to an impairment of motor facilitation. Lesion studies demonstrated that destruction of interpositus nuclei produce motor deficits including tremor, ataxia, and postural instability. Lesions of the dentate nucleus produce an impairment of the distal extremities, which becomes more evident with more complex movements.

Thus, we suggest that the abnormally reduced motor cortex excitability in our patients with the SCA lesion were induced by a disruption of a facilitatory drive from the deep cerebellar nuclei to the motor cortex via the thalamus. This hypothesis is supported by the findings in the patient with the small lesion rostral of the dentate nucleus. This lesion did not affect cerebellar hemispheres but impaired the projections originating from the deep cerebellar nuclei. In this patient, ICI, ICF, and upper limb function was affected to a similar degree as in the patients with the embolic SCA lesions.

Electrophysiological findings in the patient with the incomplete SCA infarction (case 3) indicate that ICF and ICI can be affected differentially. He had an enhanced ICI, but normal ICF, and his MRI indicated that the lesion was close to the dentate nucleus but did not destroy this area. Therefore, we suggest that ICF is particularly affected in case of lesions in the deep cerebellar nuclei or in their output. Patient 2 had a bilateral, but predominantly left-sided SCA infarction. Corresponding to this asymmetrical lesion, TMS results and motor performance were more abnormal for his left hand.

The correlation between the ICF interside ratios and the ICI interside ratios on one hand and the 9HPT as an indicator of dexterity on the other hand strongly suggest that these abnormalities of motor cortex excitability are related to the motor deficit in patients with cerebellar lesions. Thus, our electrophysiological abnormalities presumably reflect a clinical relevance of the lesion. Clinical and electrophysiological abnormalities improved during the subsequent weeks. The normalization of decreased motor excitability over time strongly suggests that the findings early after stroke onset are a lesion-induced state marker and not a trait marker.

A reduction of ICF has also been found in cerebellar degeneration and is therefore not restricted to acute vascular lesions. Because ICF was normal in patients with PICA and AICA infarctions involving the inferior parts of the cerebellum, we suggest that ICF modulations are mediated through the deep cerebellar nuclei supplied by the SCA, presumably not only in ischemic lesions but also in degenerative cerebellar diseases. In these cases, degeneration might also include the deep cerebellar nuclei.

ICI was enhanced in the patients with SCA lesions. This result is in contrast to findings in ischemic infarctions in cerebral cortex.
the territory of the middle cerebral artery. The latter are rather associated with a reduction of intracortical inhibition.23–25 This finding suggests that reduced motor excitability is not only mediated by impaired facilitation but also by exaggerated inhibition. In 1 SCA infarction, 2 PICA, 1 AICA infarction, and the lacunar lesion (cases 2, 5, 7 to 9), a relative increase of MT was found contralateral to the cerebellar lesion. These MT elevations replicate results published by Di Lazzaro et al8 and Cruz-Martinez and Arpa.8 Because these MT changes occurred independently of the type of cerebellar infarct and no association with handedness or electrophysiological parameters was found, it remains an open question which anatomical structures and physiological mechanisms are responsible for the finding. In patient 6 with a right-sided PICA infarction, MT for his right first interosseous dorsalis muscle was even lower and performance of the 9HPT was infarction, MT for his right first interosseous dorsalis structures and physiological mechanisms are responsible for the finding. In patient 6 with a right-sided PICA infarction, MT for his right first interosseous dorsalis muscle was even lower and performance of the 9HPT was faster than with his left hand. He was strictly right-handed, as tested by the Edinburgh inventory.26 Elevated motor thresholds for the nondominant hand have been found in healthy subjects.27 Thus, we hypothesize that the patient had a higher MT for his left hand muscle because this was his nondominant hand.

In cases 1, 2, 4, and 9, the SRC was less steep for the ataxic side. This may indicate an impaired recruitment of motoneurons with corticospinal projections by the TMS pulse. It suggests that corticospinal excitability can be reduced to some extent even if MTs are identical for both sides (cases 1 and 4). However, compared with the age-matched control group, SRC of the patients remained within the normal range. We conclude that intracortical excitability in primary motor cortex is more affected by a cerebellar infarction than corticospinal excitability. An alternate explanation might be that modulations of ICI and ICF are more sensitive and therefore easier to detect.

In all patients, central motor conduction times and maximum MEP amplitudes were close to the mean values of the control groups, indicating that corticospinal tract transmission was not affected by the cerebellar lesion.

In conclusion, the motor excitability abnormalities found in our patients suggest that, under normal conditions, cerebellar efferents originating from the SCA territory and passing through the deep cerebellar nuclei have an enhancing effect on motor cortical facilitation and an inhibitory effect on motor cortical inhibition.

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References

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