Motor cortex activation by transcranial magnetic stimulation in ataxia patients depends on the genetic defect

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Summary
In patients with degenerative ataxia, various abnormalities in motor cortex activation by transcranial magnetic stimulation (TMS) have been observed, including a reduction of intracortical facilitation and a lengthening of the silent period. However, the groups of patients examined in previous studies were heterogeneous, involving patients with autosomal-dominant and idiopathic cerebellar ataxia, and showing different clinical features. The aim of our present study was to investigate whether differences in motor cortex activation by TMS could be observed in genetically defined subtypes of degenerative ataxia. We examined six patients with Friedreich's ataxia, three patients with spinocerebellar ataxia (SCA) type 1, seven patients with SCA2, 12 patients with SCA3, nine patients with SCA6 and 14 healthy controls. In all subjects, motor threshold, central motor conduction time, cortical silent period after TMS, and intracortical inhibition and facilitation (as assessed by TMS using a paired pulses paradigm) were determined. Additionally, F wave amplitudes evoked by electrical peripheral nerve stimulation were measured. We found a significant reduction of intracortical facilitation in SCA2 and SCA3 patients. Furthermore, motor threshold was elevated in SCA1, central motor conduction time was lengthened in patients with Friedreich's ataxia and SCA1, and F wave amplitudes were enlarged in all the genetic subgroups except for SCA6. Silent period and intracortical inhibition did not differ between patients and controls. We conclude that changes of intracortical facilitation induced by TMS and other excitability parameters of the motor system are not a common phenomenon in degenerative ataxia, but are restricted to specific subtypes. This points to differences in the underlying pathophysiological processes in genetic subtypes of ataxia.

Keywords: spinocerebellar ataxia; Friedreich's ataxia; genetics; transcranial magnetic stimulation; intracortical facilitation

Abbreviations: CMCT = central motor conduction time; CSP = cortical silent period; FA = Friedreich's ataxia; ICI = intracortical inhibition; ICF = intracortical facilitation; MEP = motor evoked potential; SCA = spinocerebellar ataxia; TMS = transcranial magnetic stimulation

Introduction
In patients with cerebellar lesions or cerebellar degeneration, various changes in the excitability of the motor system have been observed. Using transcranial magnetic stimulation (TMS) to detect abnormalities in motor activation, motor threshold was found to be elevated in the motor cortex contralateral to a hemicerebellar lesion (Meyer et al., 1994; Di Lazzaro et al., 1994, 1995) and cortical silent period (CSP) was found to be lengthened in patients with cerebellar ataxia (Nakashima et al., 1995; Wessel et al., 1996; Liepert et al., 1998; Oechsner and Zangemeister, 1999). Using TMS under a paired pulses paradigm in patients with degenerative ataxia, a reduced intracortical facilitation (ICF) was seen, whereas intracortical inhibition (ICI) was shown to be unchanged (Ugawa et al., 1994; Liepert et al., 1998). However, the groups of patients with degenerative ataxia examined in these studies were heterogeneous, involving patients with autosomal-dominant cerebellar ataxia and idiopathic cerebellar ataxia, and showing clinical features of pure cerebellar atrophy or olivopontocerebellar atrophy.
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In autosomal-recessive Friedreich’s ataxia, the number of GAA repeats on both chromosomes is referred to as GAA1 and GAA2; in the autosomal-dominant spinocerebellar ataxias, the number of CAG repeats on the affected chromosome is referred to as CAG2. n.d. = not done. *1 = mild, 2 = moderate, 3 = severe; †1 = present, 0 = absent.
Autosomal-dominant cerebellar ataxia is increasingly characterized by the underlying genetic defects and referred to as spinocerebellar ataxia (SCA). Linkage studies revealed gene loci for SCA on chromosome 6p (SCA1) (Yakura et al., 1974), chromosome 12q (SCA2) (Gispert et al., 1993), chromosome 14q (SCA3) (Stevanin et al., 1994) and chromosome 19p (SCA6) (Zhuchenko et al., 1997). The mutations for these types of SCA have been identified as unstable expansions of CAG trinucleotide repeats in coding regions of the responsible genes (Schöls et al., 1997a). In addition, the underlying mutation of autosomal-recessively inherited Friedreich’s ataxia (FA) has been identified as an expanded GAA trinucleotide repeat in intron 1 of the X25 gene on chromosome 9q13 (Schöls et al., 1997c). Using nerve conduction and evoked potential studies, phenotypic differences between genetically distinct subtypes of hereditary ataxia have already been demonstrated (Abele et al., 1997; Schöls et al., 1997a). Studying the central motor conduction time by means of TMS, a prolongation could be observed in SCA1, but not in SCA2 or SCA3 patients (Schöls et al., 1997b; Yokota et al., 1998). In our study, we assessed various parameters of motor cortex activation by means of TMS in patients with genetically defined subtypes of ataxia in order to detect possible differences in the underlying pathophysiological mechanisms. We were especially interested in intracortical facilitation and silent period since these parameters were abnormal in heterogeneous groups of patients with cerebellar ataxia.

Methods

Patients

We examined 37 patients (13 females and 24 males) with hereditary ataxia. Patients’ mean age was 43.6 ± 13.1 years, the mean age at onset of the disease was 34.6 ± 13.6 years and the mean duration of the disease was 9.0 ± 5.8 years. By means of molecular genetic analysis, ataxia in six of these patients had been identified as FA, in three patients as SCA1, in seven patients as SCA2, in 12 patients as SCA3 and in nine patients as type 6 (SCA6). All except three patients underwent a standardized clinical examination by the same neurologist (L.S.). In all patients, signs of cerebellar dysfunction were present to a varying degree, whereas signs of pyramidal affection, bulbar involvement, peripheral neuropathy, autonomic failure or extrapyramidal signs were only found in some patients. Severity of the disease was assessed by the modified ataxia score of Klockgether (Klockgether et al., 1990) and the Barthel index (Table 1). Additionally, 14 age-matched healthy controls with no history of a neurological disease and no abnormality on physical examination were studied (five females and nine males aged between 22 and 65 years, mean 40.1 ± 13.3 years). All subjects participating in the study gave their informed consent. The study was approved by the ethical committee of the Rühr-University, Bochum.

TMS

TMS was performed using a bistim module, which was connected to two Magstim 200 stimulators (Magstim Co., Whitland, Dyfed, UK). The stimuli were applied through a circular coil (outer diameter 14 cm) positioned over the vertex with the current flowing anticlockwise in the coil in order to activate the left hemisphere predominantly. Recordings were taken from the right first dorsal interosseus muscle with Ag–AgCl surface electrodes and stored on an EMG machine (Neuropack 8; Nihon Kohden, Tokyo, Japan or Keypoint, Dantec Electronics, Skovlunde, Denmark) for further analysis. The signals were amplified with a band pass of 20 Hz–3 kHz, a sweep duration of 10–50 ms/division and a gain of 0.1–1 mV/division. The following neurophysiological parameters were determined:

Motor threshold

Motor threshold was determined at rest to the nearest 1% of the stimulator output. It was defined as the minimum intensity which produced five motor evoked potentials >50 μV out of 10 trials. The muscle relaxation was controlled acoustically.

Central motor conduction time (CMCT)

CMCT was calculated using the difference between the shortest motor evoked potential (MEP) latency of five superimposed trials after cortical magnetic stimulation and the peripheral motor conduction time. TMS was applied with an intensity of 50% above motor threshold, while the first dorsal interosseus muscle was activated with 20–30% of maximal force. Peripheral motor conduction time (PMCT) was calculated after determination of the shortest M and F wave latency of 16 trials after supramaximal electrical stimulation of the ulnar nerve at the wrist, using the formula PMCT = (M + F – 1)/2.

CSP

CSP was evoked by applying TMS 50% above motor threshold while the subject was activating the first dorsal interosseus muscle with 20–30% of maximal force. To ensure a constant activating level, the subjects had to hold a weight of 1 kg. Eight responses were rectified and superimposed. The duration of the CSP was measured from the end of the MEP (onset of EMG suppression) until the first re-occurrence of voluntary EMG activity.

ICI and ICF

ICI and ICF were determined using the paired pulses paradigm described by Kujirai et al. (1993) during complete
muscle relaxation. The second stimulus (test stimulus) was adjusted to evoke a MEP of ~1.0 mV. The conditioning stimulus was set at 80% of the individual motor threshold. Interstimulus intervals of 1, 2, 3, 4, 8, 10, 15 and 20 ms were chosen. For each interval, at least eight responses were collected. The paired pulses were mixed with a total number of 32 suprathreshold single control stimuli. The amplitude ratio of the mean conditioned MEP to the control MEP was calculated for each interstimulus interval. For further statistical analysis, parameters of ICI and ICF were defined as the averages of the MEP ratios obtained at inhibitory interstimulus intervals of 1–4 ms, and at facilitatory intervals of 8–20 ms (Ziemann et al., 1998; Schwenkreis et al., 1999).

F wave amplitudes
Sixteen F waves were elicited by supramaximal electrical stimulation of the ulnar nerve at the wrist. Peak-to-peak amplitudes were measured and the mean F wave amplitude was determined.

Statistical analysis
For each neurophysiological parameter, an unpaired t-test was performed comparing all patients with the healthy controls. For further statistical analysis, patients were divided into different subgroups following genetic or clinical criteria. Differences between the subgroups were tested using an unpaired t-test for those criteria allowing a division into two subgroups (pyramidal affection, bulbar involvement, peripheral neuropathy or autonomic failure; Table 1) and a one-way two-tailed ANOVA (analysis of variance) for those criteria allowing a division into three or more subgroups (genetic diagnosis FA, SCA1, SCA2, SCA3, SCA6; degree of cerebellar involvement: mild, moderate, severe; Table 1). Afterwards each genetically defined subgroup was compared separately with the healthy controls using an unpaired t-test. Additionally, in order to detect possible correlations, Spearman’s (ataxia score, Barthel index, number of CAG or GAA repeats) or Pearson’s (age, age at onset of the disease, duration of the disease) correlation coefficient was calculated between the clinical and neurophysiological parameters. Significance was assumed at the 5% level.

Results
Motor threshold
Motor threshold did not differ significantly between the patient and control groups (Table 2). When patients were divided into subgroups, a significant difference between genetically defined subgroups could be observed (ANOVA, $P < 0.01$). The motor threshold in SCA1 patients was significantly increased compared with healthy controls ($P < 0.001$). Regarding the individual results of the patients, one FA patient, two SCA1 patients and one SCA2 patient

<table>
<thead>
<tr>
<th>All patients</th>
<th>FA</th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
<th>SCA6</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor threshold (%)</td>
<td>55.1 ± 11.9</td>
<td>58.5 ± 10.2</td>
<td>58.0 ± 11.7</td>
<td>68.6 ± 10.9</td>
<td>80.7 ± 11.6</td>
<td>68.4 ± 11.2</td>
</tr>
<tr>
<td>Central motor conduction time (ms)</td>
<td>8.6 ± 3.0</td>
<td>8.6 ± 3.0</td>
<td>8.6 ± 3.0</td>
<td>8.6 ± 3.0</td>
<td>8.6 ± 3.0</td>
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</tr>
<tr>
<td>Cortical silent period (ms)</td>
<td>10.3 ± 4.7</td>
<td>10.3 ± 4.7</td>
<td>10.3 ± 4.7</td>
<td>10.3 ± 4.7</td>
<td>10.3 ± 4.7</td>
<td>10.3 ± 4.7</td>
</tr>
<tr>
<td>Intracortical inhibition (%)</td>
<td>19.3 ± 7.6</td>
<td>19.3 ± 7.6</td>
<td>19.3 ± 7.6</td>
<td>19.3 ± 7.6</td>
<td>19.3 ± 7.6</td>
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</tr>
<tr>
<td>Intracortical facilitation (%)</td>
<td>34.5 ± 16.0</td>
<td>34.5 ± 16.0</td>
<td>34.5 ± 16.0</td>
<td>34.5 ± 16.0</td>
<td>34.5 ± 16.0</td>
<td>34.5 ± 16.0</td>
</tr>
<tr>
<td>F wave amplitudes (mV)</td>
<td>0.39 ± 0.21</td>
<td>0.39 ± 0.21</td>
<td>0.39 ± 0.21</td>
<td>0.39 ± 0.21</td>
<td>0.39 ± 0.21</td>
<td>0.39 ± 0.21</td>
</tr>
</tbody>
</table>

Significant differences between healthy controls and patients are in bold type. n.d. = not done. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. 

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exceeded the upper limit of the normal range for the motor threshold, defined as mean ± 2 SD in normal subjects. No significant correlation between clinical (age, age at onset, duration of disease, ataxia score, Barthel index) and neurophysiological parameters could be established.

**CMCT**
CMCT was significantly prolonged in patients compared with controls ($P < 0.01$) (Table 2 and Fig. 1). Regarding genetically defined subgroups, CMCT differed significantly between these groups (ANOVA, $P < 0.001$), with significant prolongation of CMCT in FA patients ($P < 0.001$) as well as in SCA1 patients ($P < 0.05$) compared with the control group. All patients except one exceeded the upper limit of the normal range for the CMCT in both the FA and the SCA1 group, whereas the values of all other patients were in the normal range. In addition, CMCT was more prolonged in patients with signs of pyramidal affection ($P < 0.05$) and in patients with signs of peripheral neuropathy ($P < 0.05$). CMCT depended on the degree of cerebellar affection (ANOVA, $P < 0.01$) with prolonged CMCT in patients presenting with severe ataxia ($P < 0.05$). Additionally, there was a significant positive correlation between CMCT and the ataxia score ($r = 0.451$, $P < 0.05$) as well as between CMCT and the duration of the disease ($r = 0.472$, $P < 0.01$), whereas CMCT and the age at onset of the disease correlated negatively ($r = -0.518$, $P < 0.01$).

**CSP**
The SCA1 group had to be excluded from statistical analysis because, in all except one, the elevated motor thresholds did not permit a stimulation intensity 50% above threshold (Table 2). For the same reason, one FA and one SCA2 patient were also excluded. No significant differences could be observed for the cortical silent period, either between patient and control groups, or between genetic or clinical subgroups of patients. Regarding the individual results of the patients, the CSP exceeded the lower limit of the normal range in two FA patients and the upper limit in one FA, as well as in the remaining SCA1 patient. In addition, the CSP did not correlate with one of the clinical parameters.

**ICI and ICF**
Comparison between patients and healthy controls showed a significantly reduced ICF in the patient group ($P < 0.01$) (Table 2 and Fig. 2). ICF differed significantly between the genetically defined subgroups (ANOVA, $P < 0.01$). A significant reduction of ICF could be observed in SCA2 ($P < 0.001$) and SCA3 patients ($P < 0.001$) compared with healthy controls. The lower limit of the normal range was exceeded by one FA patient, five SCA2, eight SCA3 and four SCA6 patients, whereas one SCA6 patient showed an increased ICF. In clinical subgroups, no significant differences were found. In contrast, ICI did not differ significantly, either between patients and controls, or between genetic or clinical subgroups. Regarding the individual values of the patients, one SCA1 patient showed an increased ICI and one SCA2 patient a decreased ICI, whereas the values of all other patients were in the normal range. Neither ICI nor ICF correlated significantly with one of the clinical parameters.

**F wave amplitudes**
F wave amplitudes in patients were significantly enlarged ($P < 0.01$) compared with healthy controls (Table 2). However, after division of the patients into subgroups, no significant differences could be found between different subgroups. Compared with controls, F wave amplitudes showed a significant enlargement in FA ($P < 0.05$), SCA1 ($P < 0.01$), SCA2 ($P < 0.05$) and SCA3 ($P < 0.001$) patients. The F wave amplitudes of two FA, one SCA1, one SCA2, eight SCA3 and two SCA6 patients exceeded the upper limit of the normal range. A significant correlation between the F

Fig. 1 Comparison of central motor conduction time (CMCT) between groups. *Significant differences between patients and the control group.
wave amplitudes and one of the clinical parameters could not be found.

**Correlation to CAG or GAA repeats**
A significant correlation between one of the neurophysiological parameters and the number of CAG (in autosomal-dominant cerebellar ataxia) or GAA repeats (in FA) could not be established in any of the genetically defined subgroups

**Discussion**
In this study, we demonstrate the existence of abnormal motor cortex activation by TMS in some types of genetically defined ataxia, whereas other genetic subgroups show normal responses.

ICF was found to be significantly reduced in SCA2 and SCA3 patients, but not in SCA1, SCA6 or FA patients, whereas for ICI no significant alteration was found in any subgroup of ataxia patients. ICI and ICF as assessed by TMS using the paired pulses paradigm are thought to reflect the activity of intracortical inhibitory and excitatory interneuronal circuits. They are caused by separate mechanisms and originate at the motor cortical level (Kujirai et al., 1993; Ziemann et al., 1996c; Di Lazzaro et al., 1998).

In the phenomenon of ICI as assessed by TMS, a strong contribution of GABA (γ-aminobutyric acid) dependent inhibitory and a weaker contribution of NMDA (N-methyl-D-aspartate)-dependent excitatory interneuronal circuits in the motor cortex can be observed, whereas ICF is influenced by strong NMDA-dependent and weaker GABA-dependent circuits (Ziemann et al., 1996a, b; Schwenkreis et al., 1999). Additionally, ICI and ICF are modulated by various other neurotransmitters: ICI was found to be increased by dopaminergic and reduced by antidopaminergic, anticholinergic and serotoninergic drugs, whereas ICF was enhanced by antidopaminergic and anticholinergic drugs (Ziemann et al., 1997a; Werhahn et al., 1998; Liepert et al., 2001). These phenomena have been found to be altered under different pathophysiological conditions, including diseases of the motor system (Ziemann et al., 1997b) as well as basal ganglia disorders such as focal dystonia (Ridding et al., 1995b) and Parkinson’s disease (Ridding et al., 1995a) or peripheral damage such as limb amputation (Schwenkreis et al., 2000). This leads to the assumption that they underlie various influences from different brain regions and peripheral afferents able to alter their activity under pathophysiological conditions. In a heterogeneous group of patients with degenerative ataxia, ICI was found to be normal (Ugawa et al., 1994; Liepert et al., 1998), which corresponds to our findings. In contrast, ICF was found to be abnormally reduced in patients with degenerative ataxia. This contributed to a reduction of the excitatory drive of deep cerebellar nuclei to the motor cortex (Liepert et al., 1998). In SCA2 patients, neuropathological abnormalities consist of a severe Purkinje cell loss and atrophy of inferior olives, pontine nuclei and substantia nigra (Dürre et al., 1995), whereas in SCA3 patients, the cerebellar cortex and inferior olives are relatively spared, but the dentate nucleus, spinocerebellar tracts, the intermediolateral column, anterior horn cells and motor cranial nerve cells as well as the substantia nigra are severely involved (Dürre et al., 1996). SCA6 patients generally show an almost total loss of Purkinje cells, a moderate loss of granule cells, dentate nucleus neurons and inferior olives neurons, but no significant atrophy of the brainstem and no affection of basal ganglia (Zhuchenko et al., 1997). In FA, pathology is prominent in spinocerebellar and pyramidal tracts as well as in the dorsal column and dorsal root ganglia, whereas cerebellar structures are only mildly affected and basal ganglia are spared by the disease (Harding, 1984). We saw reduced ICF in SCA2 and SCA3 patients, but not in SCA6 patients who show the most ‘pure’ cerebellar involve-
ment, and also not in FA patients who have a predominantly spinal form of ataxia. This leads to the assumption that the influence of brain regions other than the cerebellar cortex and the deep cerebellar nuclei may play a more crucial role for reduced ICF. Regarding the neuropathological findings, it could be hypothesized that the reduced facilitation in SCA2 and SCA3 patients might be due to the more pronounced lesions of the substantia nigra found in these subtypes. However, this explanation seems to be rather improbable, since ICF was found to be unchanged in other diseases known to involve basal ganglia (Ridding et al., 1995a, b; Gilio et al., 2000), and antidopaminergic drugs were found to enhance rather than reduce ICF (Ziemann et al., 1997a). A possible explanation for our findings is suggested by MRI and PET studies, as well as neuropathological analysis, which demonstrated a cerebral affection outside the corticospinal tracts in SCA2 and SCA3, but not in SCA1 and SCA6 patients (Soong et al., 1997; Murata et al., 1998; Giuffrida et al., 1999; Yamada et al., 2001).

These results are consistent with a widespread expression of the SCA2 and SCA3 protein including the cerebral cortex (Paulson et al., 1997; Huynh et al., 1999). This might possibly lead to a dysfunction of the intracortical interneurons mediating facilitation as tested by paired TMS, and therefore be responsible for our findings in SCA2 and SCA3 patients. Neither in our study nor in the study by Liepert et al. (1998) could the reduced facilitation be linket to one of the patients’ clinical features. Reduced facilitation therefore may be more related to the genetic background of the disease than to one of the symptoms.

In contrast to previous studies, which found a prolongation of the CSP in patients with cerebellar degeneration (Nakashima et al., 1995; Wessel et al., 1996; Liepert et al., 1998; Oechsner and Zangemeister, 1999), this was not the case in the genetically defined ataxias investigated in this study. It therefore might not be a ubiquitous phenomenon in cerebellar degeneration. The CSP is thought to be a complex phenomenon, involving spinal mechanisms in its earlier part, and presumably cortical mechanisms in its later part (Roick et al., 1993). Activity of intracortical, presumably GABAergic interneurons, which are different from those involved in ICI seen with paired pulses TMS, seems to be crucial for the determination of its duration (Inghilleri et al., 1996; Ziemann et al., 1996a, b). It has been supposed that the prolongation of the silent period in patients with cerebellar degeneration may be caused by a release of cerebellar nuclear cells from inhibition due to a loss of Purkinje cells, which would lead to a transient facilitation of intracortical inhibitory interneurons (Wessel et al., 1996). However, this mechanism seems to be questionable, since the silent period in SCA6 patients with their almost total loss of Purkinje cells remains unchanged.

CMCT was found to be lengthened in SCA1, and even more pronounced in FA patients. This corresponds to previous reports of CMCT lengthening in subgroups of patients with degenerative ataxia (Abele et al., 1997; Cruz-Martinez and Palau, 1997; Schöls et al., 1997a, b; Yokota et al., 1998). It is explained by the involvement of the pyramidal tract in clinical as well as in necropsy studies of SCA1 and FA patients. However, pyramidal affection is also frequent in SCA3, but CMCT is not significantly altered. Interestingly, similar to the electrophysiological approach, no equivalent of spasticity has been described in post-mortem studies even in patients with gross pyramidal signs (Sequeiros and Coutinho, 1993). The significant correlations between CMCT and ataxia score, duration of the disease or age at onset, and the differences between patients with or without clinical signs of peripheral neuropathy, or between patients with different degrees of cerebellar affection may be secondary to the pronounced CMCT prolongation in FA patients, since FA patients had the youngest age at onset, the longest duration of disease and the most severe ataxia.

Motor threshold was found to be elevated only in SCA1 patients, but not in the other genetically defined subgroups. An increase in motor threshold in the contralateral motor cortex has been described in patients with a unilateral cerebellar lesion (agenesis, infarction, hemicerbellectomy) (Meyer et al., 1994; Di Lazzaro et al., 1994, 1995), whereas in patients with degenerative ataxia involving both cerebellar hemispheres symmetrically, no differences in motor threshold compared with normals have been found (Nakashima et al., 1995; Wessel et al., 1996; Liepert et al., 1998; Oechsner and Zangemeister, 1999). This corresponds to our finding of normal thresholds in most genetically defined subgroups. It is unlikely that the involvement of the pyramidal tract in SCA1 patients is the only explanation for this phenomenon, since the motor threshold was not significantly increased in FA patients. However, the exact mechanism of the threshold alteration remains unclear.

All subgroups except for the SCA6 patients showed a significant increase in F wave amplitudes compared with normals. The most prominent increase in F wave amplitudes was found in the SCA3 patients. F wave amplitudes are thought to reflect the excitability of the spinal motoneurone pool (Fisher, 1992). Since SCA6 patients present the most ‘pure’ cerebellar involvement in the disease, it can be hypothesized that the increased spinal excitability in all subgroups except for the SCA6 patients may not be due to the cerebellar degeneration. This view is supported by the report of decreased F wave amplitudes in patients with cerebellar infarctions (Drozdowski, 1995). In contrast, increased F wave amplitudes have been described in patients with spasticity resulting from an affection of the corticospinal tract (Eisen and Oodusote, 1979; Milanov, 1992), as well as in patients with an affection of the substantia nigra (Abbruzzese et al., 1985). Since at least one of these structures is affected in all SCA subtypes except for SCA6 patients, this might be the most likely explanation for our findings.

In conclusion, in this study we were able to demonstrate significant differences in parameters of motor cortex activation by TMS in patients with genetically defined subtypes of degenerative ataxia. These differences were more related to
the genotype than to clinical symptoms. This points to different pathophysiological processes in genetic subtypes of ataxia and even among the polyglutamine disorders SCA1, SCA2 and SCA3.

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References
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