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ORIGINAL COMMUNICATION

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Abnormalities of cortical excitability and cortical inhibition in cervical dystonia

Evidence from somatosensory evoked potentials and paired transcranial magnetic stimulation recordings

Abstract Cortical excitability and cortico-cortical inhibition were examined in twenty-one patients suffering from idiopathic rotational cervical dystonia. Polymyography of cervical muscles, somatosensory evoked potential recordings, and paired transcranial magnetic stimulation were used to assess the dystonic disorder. The results were compared with those obtained in a group of sixteen healthy age-matched volunteers. Statistically significant differences between the patient group and the control group were found when the amplitude values of the mean P22/N30 component measured at F [3, 4] and C[3, 4]' electrode positions were compared. The mean amplitude of P22/N30 in both of these electrode positions contralaterally to the direction of head deviation was significantly higher in the patient group ($p \leq 0.05$). The mean side-to-side P22/N30 amplitude ratio was calculated in both groups in the F[3, 4] and C[3, 4]' electrode positions: there was a significant difference between the two groups. The mean ratio (calculated contralaterally/ipsilaterally in the patient group and left/right side in the control group) was significantly higher in the patient group ($p \leq 0.05$). There were statistically significant differences between the two groups when the mean values of MEP amplitudes following paired stimuli at short and medium interstimulus intervals (ISI)) were compared. The percentage of amplitude reduction registered at short ISI was significantly lower in the patient group when both 3 ms ISI and 5 ms ISI were considered, and when the hemisphere contralateral to the direction of head deviation was stimulated. There was also a difference (with the short ISI) when the hemisphere ipsilateral to the direction of head deviation was stimulated, but this difference was not significant ($p \leq 0.5$). Almost all of the amplitude changes following the paired stimulus at the longer ISI, i. e. 10, 15, and 20 ms were significantly different when the patient group was compared with control group: when the ipsilateral hemisphere was stimulated, the amplitude of conditioned responses was significantly higher following all three paired stimuli (with 10, 15, and 20 ms ISI) at the $p \leq 0.05$ significance level; when the contralateral hemisphere was stimulated, they were significantly higher following the 10 and 20 ms ISI paired stimuli (significance level $p \leq 0.05$). The interhemispheric difference in the patient group was significant only for the paired stimuli using 3 and 5 ms (short) ISI and 15 and 20 ms (medium) ISI. There was a significantly decreased inhibition at 3 and 5 ms ISI when the hemisphere contralateral to the direction of head deviation was stimulated, as compared with the hemisphere ipsilateral ($p \leq 0.05$). Similarly, there was a significantly increased facilitation at 15 and 20 ms when the hemisphere contralateral to the direction of head deviation was stimulated, as compared with the hemisphere ipsilateral ($p \leq 0.05$). The results indicate that a disorder of both cortical excitability and intracortical inhibition exists in patients with cervical dystonia, and that this disorder is lateralized, i. e. it is located within the hemisphere contralateral to the direction of head deviation.

Key words cervical dystonia · cortical excitability · cortical inhibition · somatosensory evoked potentials · transcranial magnetic stimulation

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Introduction

The impairment of intracortical inhibition in dystonia has been extensively examined in recent years. It has been found in focal (either spontaneous or task-specific) as well as generalized types of dystonia [3, 6, 9, 11, 23, 24, 51, 52, 57]. The intracortical (or cortico-cortical) inhibition has been examined in all previous studies employing transcranial magnetic stimulation recordings and using a paired stimulation paradigm [12, 18, 27, 38, 50, 58, 63].

Similarly, a disorder of cortical excitability has been suggested in dystonia. Despite some early conflicting reports, this disorder has been found in several studies using somatosensory evoked potential recordings [17, 29, 49, 59]. Our own studies have shown that this cortical disorder in dystonia is lateralized [33, 34, 35].

It can be hypothesised, that the abnormality of cortico-subcortical loops in dystonia causes abnormality of both intracortical inhibition and cortical excitability. The aim of our study was to assess whether these two disorders exist together in patients with focal dystonia. Spasmodic torticollis was chosen for this study because of the absence of involuntary muscle activity in the target muscles when the motor evoked potentials are recorded. Muscle relaxation is very important for the recordings, and other types of focal dystonia affecting the limbs can complicate the relaxation needed for obtaining a good response. Moreover, spasmodic torticollis has a clearly lateralized character, which can also be relatively easily assessed by polymyographic recordings.

Patients and methods

All patients and healthy volunteers were well acquainted with the contents of the study and with the methods of the examination, and freely consented to participate. The study protocol was approved by the institute's ethics committee.

A total of twenty-one patients suffering from idiopathic rotational cervical dystonia were examined. Normal values were obtained by acquiring data from a group of 16 age-matched healthy volunteers. There were 8 men and 13 women in the group of patients with dystonia. The mean age in the group was 44.3 (SD = 17.8) years, the mean age at the onset of disease was 42.2 (SD = 16.8) years, and the mean duration of illness was 2.1 (SD = 1.9) years. More detailed demographic and clinical characteristics of patients' group are given in Table 1. In the group of healthy volunteers, there were 8 men and 8 women. The mean age in the group was 48.8 (SD = ± 15.5) years.

All patients underwent a thorough neurological examination before entering the study. A basic genetic study was carried out in all patients, and the character of dyskinesia was recorded on video. The Tsui score for cervical dystonia [62] was also determined for each patient. The results of clinical, biochemical and haematological examinations were normal. All patients had a MRI of the brain, which was completely normal in each case. None of the patients had been treated with botulinum toxin before the neurophysiological examinations were done.

Polymyographic recordings

Polymyographic examinations of cervical muscle activity were performed in all dystonic patients to confirm the dystonic character of the involuntary muscle contractions and the direction of the dystonic twisting, and also to elucidate the muscle pattern of dystonia and the "prime movers" of the dystonic movement. The examination protocol used in previous studies [13, 32, 33, 45] was only slightly modified. Nicolet Viking IVd (Nicolet Biomedicals, Madison, WI, U. S. A.) electromyography (EMG) equipment was used for the recordings. Patients sat quietly in a comfortable position during recordings. Muscular activity was recorded simultaneously from four channels, and all pairs of cervical muscles accessible to EMG recording were consecutively examined. Recordings were made so that all pairs of muscles examined were gradually connected with each other so that mutual relationships would be apparent. The examinations proceeded through the following cervical muscles: sternocleidomastoid, splenius capitis and cervicis, trapezius, levator scapulae, semispinales capitis and cervicis, middle scalene muscle, and the submental muscle complex (geniohyoid and mylohyoid).

Bipolar concentric needle electrodes were used in recording muscular activity. The signal was filtered in the 50–2000 Hz range. Turns/amplitude analysis and IPA (interference pattern analysis) were carried out in muscles displaying involuntary activity. Recordings were evaluated at the end of each session by a test-blind neurophysiologist, whereby the muscles fulfilling the Oestergaard and Fuglsang-Frederiksen criteria [45] were determined to be dystonic. The "prime movers", as well as the unambiguous direction of head deviation, were determined according to polymyographic and EMG patterns.

Somatosensory evoked potentials recordings

Somatosensory evoked potentials of the median nerve (SEP) were recorded in all patients with cervical dystonia and in all healthy volunteers. A Nihon Kohden Neuropack 8 device (Nihon Kohden Corp., Osaka, Japan) was used for the recordings. During recording sessions, subjects sat in a comfortable chair in a quiet, semi-darkened room. The median nerves were consecutively stimulated above their course on both wrists. Square-wave pulses lasting 0.1 ms were used at an intensity that was 1.5 times higher than the motor threshold that evoked thumb twitching. A 5-Hz stimulation frequency was used in all examinations of patients and healthy volunteers to prevent any frequency changes from influencing the amplitude of cortical SEP components [25]. SEP were recorded in the cervical spine area above the C5 vertebra, and in the Erb's point on the side of stimulated limb. The cortical components were recorded using Ag/AgCl cup electrodes in the F3, F4, C3', C4', C3 + , and C4 + electrode positions, in accordance with the International 10–20 system. For a reference, mutually connected earlobes were used. The signal was filtered in the 10–3000 Hz range, and the time base was 50 ms. Patients were instructed not to offer any resistance to dystonic head rotation during the recordings. Two runs of 2000 artefact-free sweeps were averaged in each recording session. The peaks were labelled according to the nomenclature published by Donchin and Desmedt [15]. The amplitudes between the precentral N30 peak and the previous positivity (P22), and the amplitudes between the postcentral P25 peak and the previous negativity (N20) on the scalp were measured in the superimposed runs. To prevent the impact of baseline shift on the results, the absolute values of peak amplitudes were not measured.

Mean P22/N30 in the scalp F3, F4, C3' and C4' electrode positions, and mean N20/P25 amplitude values in scalp C3 + and C4 + electrode positions were calculated in both groups after the completion of the recordings. A multivariate analysis of variance and a non-parametric Kruskal-Wallis analysis were used for the statistical analysis of results. Side-to-side ratios of P22/N30 amplitudes in the F3, F4, C3', C4'electrode positions, and side-to-side ratios of N20/P25 amplitudes in the C3 + and C4 + electrode positions were also calculated in both

groups. In the patient group, the side-to-side ratio contralateral/ipsilateral to the direction of head rotation (direction of torticollis) was calculated. In the control group, the side-to-side ratio left/right was calculated. The mean side-to-side ratios of precentral P22/N30 and postcentral N20/P25 amplitudes were calculated in both groups, and the results were compared. A multivariate analysis of variance, a non-parametric Kruskal-Wallis analysis, and a multiple range test were used for the statistical analysis.

Paired transcranial magnetic stimulation recordings

A slightly modified classical protocol was adopted for paired TMS examinations [51].The patients and controls sat comfortably, forearms resting on the arms of a chair. The magnetic stimulation was performed using two magnetic stimulators (Magstim 2000, Magstim Company Ltd, Whitland, UK) connected to a round coil (9 cm diameter; maximum magnetic field 5 T) through a Magstim Bistim module. To activate the left hemisphere, the coil was positioned at the vertex with the current flowing counter-clockwise when viewed from above, and to activate the right hemisphere, the coil was positioned at the vertex with the current flowing clockwise when viewed from above.

Paired magnetic shocks were applied in a conditioning-test paradigm using short (3, 5, and 7 ms) and medium (10, 15, and 20 ms) interstimulus intervals (ISI). Stimuli were delivered in two blocks of trials, consisting of two trials each of conditioned + single stimuli: the test shock given alone and the same shock conditioned by a conditioning stimulus at a different ISI (that is, 3–5–7 ms + control and 10–15–20 ms + control). Within each trial, paired shocks at different ISI and control single shocks were randomly intermixed and given every ten seconds. To obtain an inhibitory effect [27, 38, 51, 52, 63], the intensity of the conditioning stimulus was set at 80 % of the motor threshold (with both short and middle interstimulus intervals). The test stimulus was always delivered at 125 % of the motor threshold. The threshold was defined as the lowest stimulus intensity capable of evoking a clearly distinguishable motor evoked potential (MEP) with an amplitude of ≥ 50 μV in at least three consecutive trials, and was expressed as a percentage of the maximum stimulator output. All stimuli were delivered through the Bistim module, which normally reduces the stimulator output by ≈30 %. Therefore, the actual intensity values are ≈30 % lower than those shown on the stimulator display. The threshold for eliciting responses was assessed with the target muscle completely relaxed. To help the subject maintain relaxation, audiovisual feedback was given through EMG equipment (EMG signal was visualized on the equipment display and also monitored using an EMG speaker). MEP were registered from the first dorsal interosseal muscle, contralateral to the side of stimulation, using a pair of Ag/AgCl surface electrodes. Responses were amplified, filtered, bandpassed in the 3–1000 Hz range, digitised using the Nihon Kohden Neuropack 8 device (Nihon Kohden Corp., Osaka, Japan) and stored using the Cambridge 1401 laboratory interface (Cambridge Lab Design, Cambridge, UK) for later off-line analysis. The MEP amplitude was measured peak-to-peak to avoid the impact of baseline shift on the results, and the MEP were expressed as a percentage of the response to unconditioned control shock. The results of eight trials for each ISI were collected and averaged. A multivariate analysis of variance, a non-parametric Kruskal-Wallis analysis, and a multiple range test were used for the statistical analysis of results.

Results

The results are presented in Tables 1 to 4, and in Figures 1 and 2.

All twenty-one patients suffered from rotational torticollis. Ten patients suffered from left-sided torticollis,

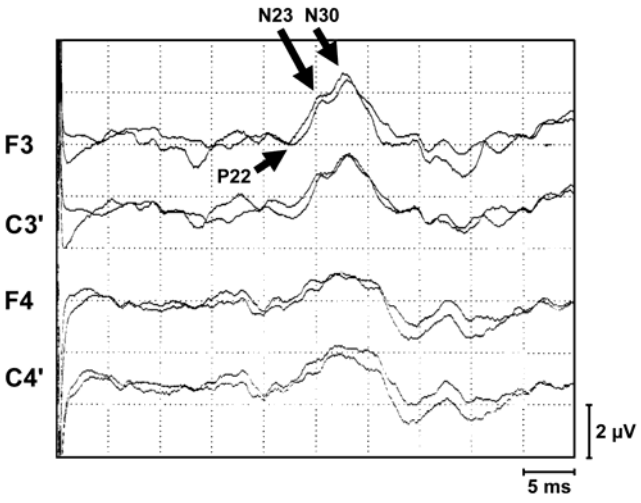

Fig. 1 An example of the precentral cortical components of the median nerve somatosensory evoked potentials in the patient suffering from right-sided torticollis. Note the increased P22/N30 amplitude above the left hemisphere, contralaterally to the direction of head deviation. Time base: 5ms/division, amplitude: 2 μV division. The two runs of 2000 artifact-free sweeps were superimposed.
F(3,4) precentral electrode positions in the International 10–20 system; *C(3,4)'* precentral electrode positions in the International 10–20 system; *P22, N23, N30* precentral cortical SEP components; *μV* microvolts; *ms* milliseconds

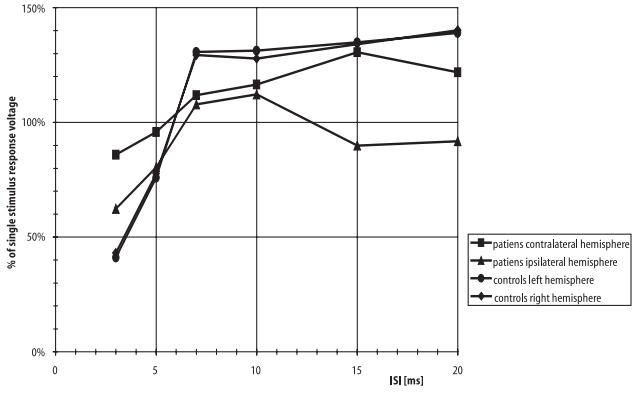

Fig. 2 The graph illustrating the percentage of single shock response amplitude value at different interstimulus intervals (ISI) in the groups of patients and healthy control subjects above both hemispheres. Contralateral/ipsilateral hemisphere to the direction of head deviation (in the patient's group) and left/right hemisphere (in the control group) were stimulated. X-axis: different ISI, Y-axis: percentage of single shock response amplitude reduction.

and eleven suffered from right-sided torticollis. The splenius capitis muscle, ipsilateral to the direction of head deviation, was considered the "prime mover" or "leading muscle" of cervical dystonia in twelve patients. The sternocleidomastoid muscle, contralateral to the direction of head deviation, was considered the "prime mover" or "leading muscle" of cervical dystonia in six patients. The contralateral trapezoid muscle was considered the "prime mover" or "leading muscle" of cervical dystonia in four patients. However, these three muscles

Table 1 Patients' demographic and clinical characteristics

Pat. Nr.	Sex (M/F)	Age at exam. (years)	Age at dystonia onset (years)	Duration of illness (years)	Type of dystonia	"Prime movers"	Another neurological abnormality
1	F	59	57	2	Torticollis right	**SPL right** TRP left	– –
2	F	35	31	4	Torticollis right	**TRP left** SPL right	– –
3	M	39	38	1	Torticollis right	**SPL right** SCM left	– –
4	F	41	38	3	Torticollis right	**SPL right** TRP left	Bilateral hand tremor
5	F	60	59	1	Torticollis right	**SPL right** SCM left	– –
6	F	41	39	2	Torticollis left	**SCM right** SPL left	– –
7	F	47	45	2	Torticollis left	**SPL left** TRP left	– –
8	F	44	37	7	Torticollis left	**SCM right** SPL left	– –
9	M	40	39	1	Torticollis left	**SCM right** SPL left	– –
10	M	30	29	1	Torticollis left	**SCM right** SPL left	– –
11	F	63	60	3	Torticollis right	**SCM left** SPL right	– –
12	F	30	28	2	Torticollis right	**TRP left** SPL right	– –
13	F	49	48	1	Torticollis left	**SPL left** TRP right	Bilateral hand tremor
14	F	60	59	1	Torticollis left	**TRP right** SPL left	– –
15	F	64	61	3	Torticollis right	**SPL right** SCM left	– –
16	M	47	46	1	Torticollis left	**SPL left** SCM right	Voice tremor
17	M	20	18	2	Torticollis left	**SPL left** TRP right	– –
18	F	55	52	3	Torticollis right	**SCM left** SPL right	– –
19	M	30	29	1	Torticollis right	**SPL right** SCM left	– –
20	M	56	54	2	Torticollis left	**SPL left** SCM right	– –
21	M	20	19	1	Torticollis right	**SPL right and** TRP left	– –

Pat.Nr. patient's number; *M* male; *F* female; *age at exam* patient's age at the time of examination; *prime movers* the muscles identified by the polymyographic and EMG examination to be the most active in dystonic movements, one of them being determined to be the "prime mover"; *SPL* splenius capitis muscle; *SCM* sternocleidomastoid muscle; *TRP* trapezoid muscle

were involved in dystonic dyskinesia in all patients. Other muscles involved were: the levator scapulae muscle in three patients; the semispinalis capitis muscle in one patient; and the splenius cervicis muscle in one patient; none of these muscles served as the "prime mover" or "leading muscle" of cervical dystonia.

There were statistically significant differences in the results of somatosensory evoked potentials of median nerve recordings between the patient group and the control group when the mean P22/N30 component amplitude values measured at F [3, 4] and C [3, 4]' electrode positions were compared. The mean amplitude of P22/N30 in both electrode positions contralateral to the direction of head deviation was significantly higher in the patient group ($p \leq 0.05$). When the mean amplitude values measured in the F [3, 4] and C [3, 4]' electrode po-

Table 2 The mean P22/N30 and N20/P25 median SEP component amplitude values in the cervical dystonia patient group and the healthy control subject group

Group	Mean amplitude value P22/N30 in μV (± SD)				Mean amplitude value N20/P25 in μV (± SD)	
	F(3,4)		C(3,4)′		C(3,4)+	
	Contralaterally	Ipsilaterally	Contralaterally	Ipsilaterally	Contralaterally*	Ipsilaterally*
Patients	1.91 (0.82)	1.16 (0.59)	1.74 (0.72)	1.12 (0.61)	2.12 (0.53)	2.32 (0.75)
Controls	1.23 (0.75)	1.22 (0.67)	1.12 (0.71)	1.24 (0.78)	2.26 (0.59)	2.15 (0.34)

* the values for the group of healthy control subjects were calculated above the left hemisphere (contralaterally) and right hemisphere (ipsilaterally). This pattern was chosen because of the left hemispheric dominance in the control group.
P22/N30 precentral cortical component of median nerve SEP; *N20/P25* postcentral cortical component of median nerve SEP; *μV* microvolts; *SD* standard deviation; *F(3,4), C(3, 4)′* precentral electrode positions, according to the International 10–20 system; *C(3,4)+* postcentral electrode positions, according to the International 10–20 system

sitions ipsilateral to the direction of head deviation were compared, the difference was not significant (even at the level $p \leq 0.5$). The mean side-to-side P22/N30 amplitude ratio was calculated in both groups in the F [3, 4] and C [3, 4]'electrode positions, and there were significant differences. The mean ratio (calculated contralaterally/ipsilaterally in the patients and left/right side in the controls) was significantly higher in the patient group ($p \leq 0.05$). The differences between both groups when the amplitudes of the N20/P25 postcentral median SEP component were recorded and measured were not significant. The same finding was revealed when the mean side-to-side N20/P25 amplitude ratio was compared in both groups.

Table 3 The mean values of side-to-side amplitude ratio of P22/N30 and N20/P25 median SEP component in the cervical dystonia patient group and the healthy control subject group

Group	Mean side-to-side ratios contralaterally/ipsilaterally		
	P22/N30		N20/P25
	F(3,4)	C(3,4)′	C(3,4)+
Patients	1.81 (0.51)	1.58 (0.29)	0.98 (0.25)
Controls	1.02 (0.23)	1.12 (0.34)	1.04 (0.16)

* the values in the control group were calculated as the ratio of values measured above the left hemisphere (contralaterally) and right hemisphere (ipsilaterally). This pattern was chosen because of the left hemispheric dominance in the control group.
P22/N30 precentral cortical component of median nerve SEP; *N20/P25* postcentral cortical component of median nerve SEP; *μV* microvolts; *SD* standard deviation; *F(3,4), C(3, 4)′* precentral electrode positions, according to the International 10–20 system; *C(3,4)+* postcentral electrode positions, according to the International 10–20 system

There were statistically significant differences in the results of paired TMS registration between both groups when the mean values of the MEP amplitudes following paired stimuli at both short and medium interstimulus intervals were compared. The percentage of amplitude reduction registered at short ISI was significantly lower in the patient group when both 3 ms ISI and 5 ms ISI were considered, and when the hemisphere contralateral to the direction of head deviation was stimulated. There was also a difference (with the short ISI) when the hemisphere ipsilateral to the direction of head deviation was stimulated, but this difference was not significant ($p \leq 0.5$). Almost all of the amplitude changes following the paired stimulus at longer ISI, i. e. 10, 15, and 20 ms were significantly different when the patient group was compared with control group: when the ipsilateral hemisphere was stimulated, the amplitude of conditioned responses was significantly higher following all three paired stimuli (with 10, 15, and 20 ms ISI) at the level p

Table 4 The mean values of conditioned MEP (measured peak-to-peak), recorded using different interstimulus intervals (ISI) when the hemispheres contralateral and ipsilateral to the direction of head deviation were stimulated, in both the patient and control groups. The responses were measured above the first interosseal muscle, and are expressed as a percentage of the value of single shock response alone (± SD)

ISI (msec)	Mean percentage of single test stimulus response alone in the patient group and the control group at different ISI (percentage ± SD)			
	Patients		Controls	
	Contralaterally*	Ipsilaterally**	Contralaterally•	Ipsilaterally••
3	85.9 (15.5)	62.3 (19.8)	41.1 (20.9)	43.1 (18.5)
5	95.8 (32.2)	80.4 (22.9)	75.9 (10.2)	77.7 (9.4)
7	111.9 (38.8)	107.9 (22.3)	130.7 (15.8)	129.4 (16.3)
10	116.5 (10.0)	112.2 (13.9)	131.3 (17.4)	127.8 (19.9)
15	130.6 (16.3)	89.9 (5.6)	134.9 (21.3)	134.1 (24.6)
20	121.8 (12.5)	91.8 (5.9)	139 (20.1)	140.2 (16.1)

*, ** indicates that the hemisphere contralateral or ipsilateral to the direction of head deviation was stimulated.
•, •• the values in the group of healthy control subjects were measured when the left hemisphere (contralaterally) and right hemisphere (ipsilaterally) were stimulated. This pattern was chosen because of the left hemispheric dominance in the control group.
SD standard deviation; *ISI* interstimulus interval (in milliseconds)

≤ 0.05; when the contralateral hemisphere was stimulated, they were significantly higher following the 10 and 20 ms ISI paired stimuli ($p \leq 0.05$). The interhemispheric difference in the patient group was significant only for the paired stimuli using 3 and 5 ms (short) ISI and 15 and 20 ms (medium) ISI. There was a significantly decreased inhibition at 3 and 5 ms ISI when the hemisphere contralateral to the direction of head deviation was stimulated, as compared with the ipsilateral hemisphere ($p \leq 0.05$). Similarly, there was a significantly increased facilitation at 15 and 20 ms ISI when the hemisphere contralateral to the direction of head deviation was stimulated, as compared to the ipsilateral hemisphere ($p \leq 0.05$). There were no significant differences when the amplitudes of paired responses were compared between both hemispheres in the control group.

Discussion

It is hypothesised that certain parts of premotor cortex areas serve as an important substrate in the process of movement preparation. The most frequently mentioned of these are the dorsolateral prefrontal cortex (DLPC) and the supplementary motor area (SMA), which are defined as Brodmann areas 6, 8, and 9. It is also believed that abnormal basal ganglia outputs can induce abnormalities or alter cortical excitability and inhibition in these locations [2, 20, 49, 52]. The role of midbrain nuclei has been also discussed [37].

We found both cortical functions significantly altered in patients with cervical dystonia. This fact only provides further evidence, following the recent similar findings of other authors [17, 18, 23, 29, 49, 51, 52, 59] and of our previous studies involving SEP recordings [33, 34, 35]. SEP recordings in focal dystonia (and in other types of dystonic disorders) indicate that SEP changes can represent a disorder of cortical excitability in motor areas. This disorder seems to be lateralized, depending on the side of body involvement by dystonia [17, 33–35]. Our results in the examined group of twenty-one patients with rotational cervical dystonia provide further evidence of this. It can be presumed that the lateralization is caused by a relatively higher amplitude of precentral P22/N30 on the side contralateral to the direction of head rotation. This higher amplitude could be the consequence of (abnormally) high excitability in this part of the cortex, which generates precentral SEP components [49, 55]. The cause of this enhanced excitability is probably the dystonic motor disorder in the basal ganglia and their loops [2, 20, 57].

Recent positron-emission tomography (PET) studies have supported the existence of a specifically patterned increased cortex excitability in dystonia. A PET study examining dystonic patients performing voluntary movements showed increased bilateral activity in the rostral SMA, in the lateral premotor cortex contralateral to the performing limb, and bilaterally in the lentiform nucleus [8, 46, 47]. A similar activation pattern has been found in other studies, and some studies found decreased activation of the dorsolateral prefrontal cortex ipsilateral to the active limb [16]. From an anatomical point of view, this means that the increased cortical activation was repeatedly found in regions where the F [3, 4] and C [3, 4]' electrodes were placed during median SEP recordings. In the light of our results in twenty-one patients with rotational dystonia, we could conclude that the increased amplitude of precentral components is a correlate of the increased cortical excitability in the premotor cortical areas, which is specifically lateralized.

The disorder of intracortical (or cortico-cortical) inhibition in patients with dystonia has been found and later confirmed in several studies dealing with different types of dystonia [6, 18, 23, 51, 52]. This disorder has been investigated using different target muscles; some studies with a conditioned silent period have also used cervical muscles for the assessment of MEP amplitude. Ridding et al. and Rona et al. found inhibition of the test response at intervals shorter than 7 ms in relaxed and also in active muscles. However, in the active muscle the inhibition was less expressed [51, 52]. Ridding et al. studied patients with writer's cramp, and found significantly less inhibition in patients at 3 and 5 ms intervals [51]. Rona et al. studied 3–20 ms intervals in a group of patients with different types of dystonia and during voluntary muscle activation [52]. Both of Rona et al.'s groups (patients and controls) showed only partial suppression at 3 and 5 ms intervals, and essentially no variation at the subsequent intervals. This inconsistency can probably be explained by more than the different techniques of stimulation and different types of coil used. The patients of Ridding et al. [51] were stimulated with the target muscle at rest, whereas the patients of Rona et al. [52] were tested during monitored voluntary contraction of the target muscle. Another difference concerns the patient population. Ridding et al. studied patients with writer's cramp, a focal task-specific dystonia, with which the patients may be presumed to show abnormal muscle activity only during the task. Rona et al. studied a mix of patients suffering from either segmental or generalized dystonia, with affected target muscles, and these patients could relax not only the target, but all the affected muscles only with difficulty. A precise comparison of these (most frequently cited) studies in dystonic patients is therefore not possible.

We studied these phenomena in patients suffering from cervical dystonia, who were able to relax completely the target muscles, and in an age-matched group of healthy individuals. In the control group, we obtained practically the same results as previous investigators [18, 27, 50–52, 63]. In the group of patients, we found a clear abnormality of test response suppression. The

MEP responses following the paired shocks with short ISI (3 and 5 ms) were significantly less expressed or were "defectively" depressed in the patient group, in comparison to the control group. This abnormality was present following the stimulation of both hemispheres, as compared to control group. In other words, it was bilateral. However, the abnormality was more expressed in one hemisphere. This hemisphere was contralateral to the direction of head deviation, which means contralateral to the splenius capitis and trapezius muscles and ipsilateral to the sternocleidomastoid muscle active in the dystonic movement.

This inter-hemispheric difference was also expressed in the level of statistical significance ($p \leq 0.05$, and $p \leq 0.01$, respectively) when compared with the corresponding hemispheres in the control group. In light of our repeated findings in torticollis patients using SEP examinations [33–35], this is probably a similar finding, indicating that cortical abnormality is lateralized in rotational torticollis. It seems that both cortical excitability (reflected in abnormal SEP amplitudes) and intracortical inhibition (reflected in abnormal conditioned MEP responses) share the same lateralization pattern, i. e. they are both present (or at least more expressed) in the cortex of the hemisphere contralateral to the side of head deviation (should the direction of head deviation be expressed in terms of dystonic body involvement, it is the same side that is predominantly affected by dystonia). The hemisphere contralateral to the direction of head deviation in torticollis is that in which the cortical representation of "prime movers" (i. e. the splenius capitis muscle, the sternocleidomastoid muscle, and the trapezoid muscle) lies. This has been confirmed not only in our previous polymyographic study [32], but also in other studies, mainly with transcranial magnetic stimulation [4, 5, 36, 41, 43, 44].

The lateralized cortical involvement in dystonic disorders has been reported several times, using diverse methods of assessments: in our SEP studies [33–35]; in the study of Tinazzi et al., using tibial SEP recordings [59]; in the study of Naumann and Reiners, using long-latency reflex examination [42]; in the studies of Grünewald et al. and Yoneda et al., where the tonic vibration reflex was studied [19, 64]; and recently, in the study of Frasson et al., using conditioned median SEP recordings [17]. The lateralized abnormality, respective of the body side pattern of dystonia, was also found in Deuschl et al. studies of movement related cortical potentials (MRCP) [14] and Ikeda et al. and Hamano et al. studies of contingent negative variation (CNV) [22, 26]. Neuroimaging studies have also provided evidence that the cortical pattern of involvement in dystonia is lateralized, and cortical abnormality seems to be predominantly contralateral to the body part affected by dystonia [8, 16, 46, 47].

The increased cortical excitability and mutual impairment of cortico-cortical (or intracortical) inhibition is supposed to be caused by the abnormal afferent flow from intrafusal fibres through the Ia afferents [21, 22, 30, 33–35, 48]. This hypothesis is strongly supported by observations of changes induced by successful botulinum toxin treatment. It has been recently shown that a blockade of intrafusal fibres, induced by BTX-A, can change the afferent flow in Ia fibres, and modulate (or "normalize") the characteristics of cortical disorders. This has been demonstrated for both cortical excitability [34, 41] and intracortical inhibition [18]. On the other hand, the changes of electrical and metabolical characteristics of the brain cortex in dystonia following BTX-A treatment are probably quite different, as has been demonstrated by PET studies, where no observable changes were present following treatment of lateralized focal dystonia [7].

Current concepts and hypotheses of the origin of dystonic disorder indicate that dystonia is not purely a motor disorder, as was originally supposed [39]. It is also probably not exclusively a sensory disorder, as was speculated a few years ago [21, 30]. The affliction of several brain areas in dystonia seems to be more complex, involving both motor and sensory loops. From the integrative point of view, it should instead be viewed as a disorder of sensorimotor integration, as has been recently proposed [1, 10, 31, 54, 60, 61]. This concept is rather new, but it corresponds well with the pathophysiological hypotheses that were published over ten years ago, which employed a more complex, organic-behavioural view of dystonic disorders [28, 53]. We feel that a more detailed correlation of neurophysiological examinations, in conjunction with PET and particularly with fMRI studies, done on homogeneous groups of dystonic patients, could in the near future bring further proof supporting these "old", but surprisingly modern hypotheses.

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