

Abnormal cortical processing of voluntary muscle relaxation in patients with focal hand dystonia studied by movement-related potentials

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Summary

In order to clarify the abnormality in cortical motor preparation for voluntary muscle relaxation of the hand in patients with focal hand dystonia, Bereitschaftspotentials (BPs) preceding voluntary muscle contraction and relaxation were recorded in eight patients (three with simple writer's cramp and five with dystonic writer's cramp), and were compared with those from 10 normal subjects. Voluntary muscle relaxation: after keeping the right wrist in an extended position for > 5 s, the subject let the hand drop by voluntarily terminating muscle contraction of the wrist extensor without any associated muscle contraction. Voluntary muscle contraction: the right wrist was flexed by voluntarily contracting the wrist flexor muscle. Scalp EEGs were recorded from 11 electrodes placed over the frontal, central and parietal

areas. In the control group, the BP measured at the movement onset was maximal at the left central area (C1), and distributed predominantly over the left hemisphere equally in both the contraction and relaxation tasks. In the focal hand dystonia group, BP was maximal at C1 in the contraction task, whereas, in the relaxation task, it was maximal at the midline central area (Cz) and symmetrically distributed. At the left central area, the BP amplitude in the focal hand dystonia group was diminished significantly in the relaxation task compared with the contraction task ($P < 0.05$). The present results demonstrate for the first time that the cortical preparatory process for voluntary muscle relaxation, or motor inhibition, is abnormal in focal hand dystonia.

Keywords: focal hand dystonia; central motor control; voluntary muscle relaxation; movement-related cortical potential

Abbreviation: ANOVA = analysis of variance; BP = Bereitschaftspotential; MP = motor potential; MRCP = movement-related cortical potential; SI-MI = primary sensorimotor cortex; SMA = supplementary motor area; TMS = transcranial magnetic stimulation

Introduction

Dystonia is defined as a syndrome of sustained muscle contraction, frequently causing twisting and repetitive movements, or abnormal postures (Fahn, 1988). Dystonic movements typically are aggravated by an attempt to perform an action (Oppenheim, 1911). Recently, physiological studies suggested an abnormality in the cortical motor control system in patients with dystonia. PET studies in patients with dystonia of various forms showed hypometabolism of glucose in the basal ganglia, thalamus and prefrontal association cortices (Karbe *et al.*, 1992), and diminished blood flow changes in the sensorimotor and supplementary motor areas in response to various activation tasks (Tempel and Perlmutter, 1990, 1993; Ceballos-Baumann *et al.*, 1995, 1997). An

abnormal cortical sensorimotor integration mechanism was also shown by using electrophysiological methods (Kaji *et al.*, 1995a; Ikeda *et al.*, 1996) and a biokinetic approach (Odegren *et al.*, 1996).

Movement-related cortical potential (MRCP) preceding self-paced, repetitive voluntary muscle contraction consists of at least two slow negative shifts (Kornhuber and Deecke, 1965; Shibasaki *et al.*, 1980). The early part [Bereitschaftspotential (BP) or NS1] is maximal at the central vertex and symmetrically distributed over the scalp, whereas the later part (NS' or NS2) is larger at the central area contralateral to the movement (Shibasaki *et al.*, 1980). These potentials are known to reflect a central motor control process in

humans, and a number of studies employed this technique to investigate the mechanism of movement disorders (Deecke *et al.*, 1977; Shibasaki *et al.*, 1978; Barrett *et al.*, 1986; Dick *et al.*, 1989). Abnormalities of MRCP were reported in patients with various types of dystonia. Fève *et al.* showed diminished MRCP amplitude during wrist flexion in 15 patients with dystonia due to lesions in the basal ganglia and thalamus (Fève *et al.*, 1994). In patients with idiopathic torsion dystonia, in addition to the diminished amplitude of NS' at the midline leads compared with normal controls, its horizontal distribution for the finger extension task was not lateralized to the hemisphere contralateral to the movement (Van der Kamp *et al.*, 1995). Deuschl *et al.* also showed significant diminution of NS' over the central area contralateral to the movement in patients with writer's cramp (Deuschl *et al.*, 1995). These MRCP studies suggest impaired activation of the sensorimotor cortex contralateral to the affected hand just before making a voluntary movement, regardless of the kind of dystonia.

Since patients with dystonia suffer from sustained, abnormal muscle contraction during voluntary actions, a disturbance of an inhibitory mechanism of motor output has been proposed in this condition. Transcranial magnetic stimulation (TMS) enabled us to evaluate both excitatory and inhibitory functions of the corticospinal tracts (Barker *et al.*, 1985; Mills, 1988; Kujirai *et al.*, 1993; Wassermann *et al.*, 1993). The physiological corticocortical and corticospinal connections for voluntary inhibition of muscles are still unclear even in normal subjects, but the fact that the pathological process in motor neuron disease differentially influences the inhibitory and excitatory motor effects of TMS suggests that different corticospinal pathways may mediate these two types of responses in human (Triggs *et al.*, 1992). In patients with dystonia, an abnormality of the silent period evoked by TMS has been reported (Mavroudakis *et al.*, 1995), suggesting an impairment of not only excitatory but also inhibitory corticospinal pathways. In addition, paired magnetic stimulation given to the motor cortex contralateral to the affected hand in patients with focal dystonia also showed a decrease in the early corticocortical suppression which, in normal subjects, is usually seen when tested with short interstimulus intervals (Ridding *et al.*, 1995) as well as with relatively longer interstimulus intervals (Rona *et al.*, 1998). Furthermore, by also using TMS in patients with cervical dystonia (Odegren *et al.*, 1997) and in a patient with dystonia secondary to a putaminal lesion (Hanajima *et al.*, 1994), a disturbance of the cortical inhibitory regulation of neuronal excitability was demonstrated. However, these stimulation studies have not addressed directly the mechanism underlying *voluntary* inhibition of muscle contraction (muscle relaxation task in the present study) in focal dystonia.

Some of the present authors studied MRCP preceding voluntary relaxation of hand muscle in normal subjects, and compared it with that preceding a similar movement,

caused by muscle contraction (Terada *et al.*, 1995). There was no significant difference in the MRCPs with respect to the waveform and scalp distribution between voluntary relaxation and active contraction of the hand muscle (Terada *et al.*, 1995). Taking into account the results of subdural recording of MRCP associated with muscle contraction in epileptic patients (Neshige *et al.*, 1988; Ikeda *et al.*, 1992), the above findings were interpreted to suggest that the primary sensorimotor cortex (SI-MI) and supplementary motor area (SMA) are also active before voluntary muscle relaxation. In our recent subdural recording, the MRCP preceding voluntary muscle relaxation was clearly observed in the SMA, similarly to that preceding voluntary muscle contraction (Yazawa *et al.*, 1998). Therefore, in the present study, we aimed at clarifying the pathophysiological mechanism underlying muscle relaxation in patients with focal hand dystonia, by recording the MRCP preceding voluntary relaxation of the hand muscle.

Material and methods

Patients

Nine patients (five men and four women) with focal dystonia of the right hand, mainly complaining of difficulty in writing, participated in this study. They were divided into two groups according to previous studies (Sheehy and Marsden, 1982; Kaji *et al.*, 1995b). The symptoms in three of the patients appeared only at the time of writing (simple writer's cramp), and in the remaining six patients symptoms occurred both on writing and in association with other hand tasks (dystonic writer's cramp). The mean age of the patients was 32.2 years (SD 7.2 years) and the mean duration of illness was 4.1 years. For the present study, we excluded patients older than 40 years in order to avoid a possible ageing effect (Barrett *et al.*, 1986). All patients originally were right-handed, but one patient had acquired left hand writing before this experiment. No patient had other neurological disorders. All patients and control subjects gave informed consent after a full explanation of the purpose of this study. The study was approved by the Ethics Committee of Kyoto University School of Medicine. The electrophysiological data obtained were compared with those obtained from 10 normal subjects [eight men and two women, mean age 30.3 years (SD 6.2 years), seven right-handed and one left-handed] who had been studied previously by the authors' group, using exactly the same methods (Terada *et al.*, 1995).

Movement paradigms

Subjects were seated in a reclining arm chair in a quiet room with their eyes kept open and fixating forward at the target placed 1.5 m in front of them during the recording session. Each subject performed two motor tasks:

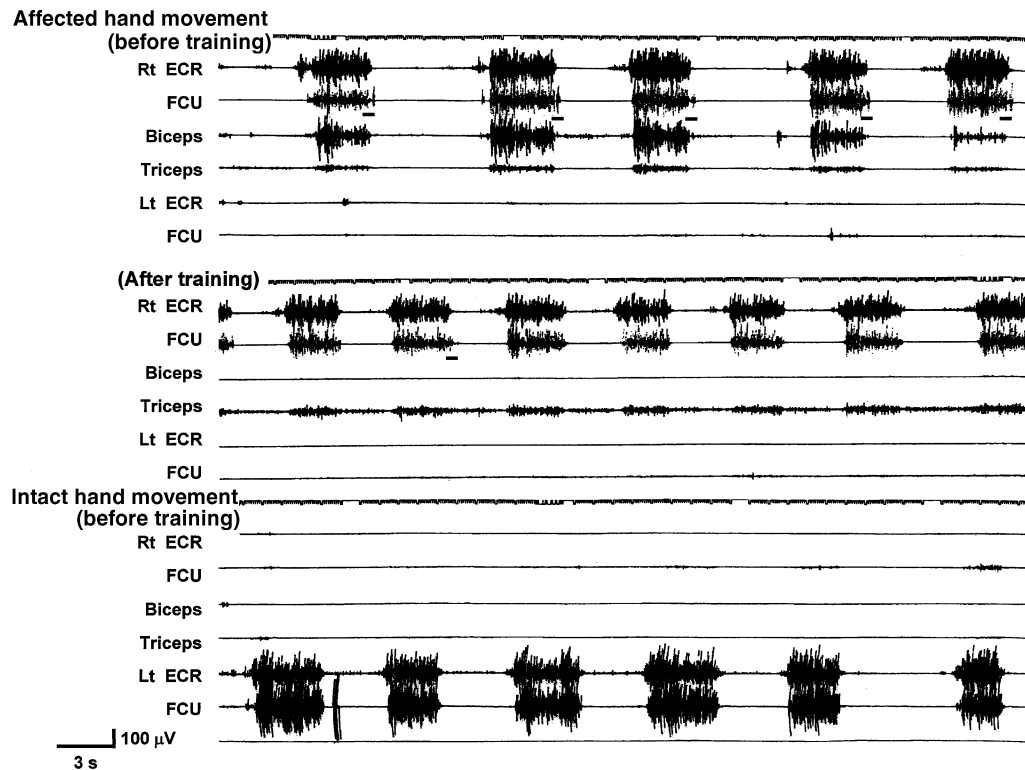


Fig. 1 A sample of surface EMGs during a training session of the muscle relaxation task in a patient with focal hand dystonia. In the movement of the affected (right) hand, before training (top), additional muscle activities were observed in the flexor carpi ulnaris muscle when the subject tried to relax the extensor carpi radialis muscle (underlined). The patient could achieve complete performance after 6 min training (middle). In contrast, he could do the task well with the intact hand even without training (bottom). ECR = extensor carpi radialis muscle; FCU = flexor carpi ulnaris muscle; Lt, left; Rt, right.

'relaxation' and 'contraction' with the right hand (affected side in all patients) according to the previously described method (Terada *et al.*, 1995). In the relaxation task, the right forearm was put on a paper board placed on the arm rest of the chair, with the hand pronated palm downwards. The subject was requested to keep the right wrist in extension to 20–30° for at least 5 s before each movement task, and then to let it drop by voluntarily terminating the contraction of the wrist extensor muscle. Once the relaxation was achieved, the subject maintained the relaxed position for at least 5 s and then resumed the extended position of the wrist for the next trial. Before data acquisition, all subjects practised the task so that the surface EMG activity was restricted only to the extensor carpi radialis muscle or in some cases to the extensor carpi radialis and the flexor carpi ulnaris throughout the extended position. As in the previous study (Terada *et al.*, 1995), the polygraphic surface EMG was monitored to ensure that the hand had dropped without associated contraction of any muscles in either the affected or unaffected hand (Fig. 1). During the initial training phase for the affected hand, some contraction of the flexor carpi ulnaris muscle was seen in association with the hand drop (underlined in Fig. 1). In the training session for the

unaffected hand, eight out of nine subjects were able to relax voluntarily the extensor carpi radialis muscle satisfactorily, even without training. Since one subject constantly showed additional EMG activity in the flexor carpi ulnaris and triceps brachii muscles during the relaxation task in the movement of the dystonic and the intact hand, his data were excluded from further analysis.

In the contraction task, the forearm was placed perpendicular to the paper board, with the ulnar side down. The subject flexed the wrist by voluntarily contracting the wrist flexor muscle as quickly as possible, and kept the flexed position for >5 s. Then, the wrist was returned to the relaxed, neutral position for the next trial. Although, in the previous study of normal subjects (Terada *et al.*, 1995), the degree of wrist flexion was controlled to 20–30°, some patients in the present study could not control it to a consistent degree, and they tended to flex the wrist to an excessive degree. For the repetition rate, the subjects were instructed so that the rate for the contraction task was kept the same as for the relaxation. Each recording session consisted of 50 trials of the same task, and each patient underwent three sessions each for the relaxation and contraction tasks, which were carried out in a counterbalanced order across the subjects. The task

performance was monitored and stored by a video camera system, as were the EMG recordings (see below).

Data acquisition

For recording EEGs, 11 Ag/AgCl shallow cup electrodes (F3, Fz, F4, C3, C1, Cz, C2, C4, P3, Pz and P4) (American EEG Society, 1992) were fixed to the scalp with collodion, and all electrodes were referenced to linked earlobe electrodes. EOG was monitored simultaneously by an Ag/AgCl cup electrode placed at the right inferior lateral canthus referenced to the right earlobe electrode. The impedance of all electrodes was kept $< 5 \text{ k}\Omega$. The bandpass filter was set to 0.05–100 Hz for both EEGs and EOGs.

In order to monitor the contraction and relaxation of the corresponding muscle as well as to detect concomitant contraction of other muscles, if any, EMGs were recorded by a pair of Ag/AgCl cup electrodes placed 3 cm apart on the skin overlying each of the extensor carpi radialis, flexor carpi ulnaris, biceps brachii and triceps brachii muscles, all bilaterally (Fig. 1). The bandpass filter for recording EMGs was set to 20–100 Hz.

To determine the movement onset, an accelerometer (AS-2GA, Kyowa Electronic Instruments, Co.) was fixed to a light paper plate which was bound on the dorsal aspect of digits II–V by tapes. The low frequency filter was set to 0 Hz (DC), and the high frequency filter to 100 Hz. The accelerogram was rectified and used to obtain the fiducial point for averaging the EEG and EOG as described below.

All segments of the amplified signals covering 2.4 s before and 1.2 s after the movement onset were stored on a computer (DP1100, NEC San-Ei) at a sampling rate of 333 Hz for the subsequent off-line analysis.

Data analysis

After completing all sessions for each subject, the EEG, EOG, EMG and accelerogram for each trial were displayed on a cathode ray tube monitor, and the precise onset of the movement was determined visually on the rectified accelerogram. If there was any artefact caused by eye movements or other sources, or if EMG activities in inappropriate muscles were recognized, that trial was eliminated from further analysis.

After confirming the reproducibility of the averaged waveforms among different sessions of the same movement task, a group average for each task was obtained with respect to the movement onset for each subject. Then, a grand average for each task was obtained by averaging the group average data of like sessions across all subjects. The baseline was corrected by subtracting the average value of the initial 166 points (499 ms) from the waveform for each channel.

The onset of the slow negative pre-movement shift, which was defined as the time when the baseline began deflecting toward negativity at electrode Cz, was determined visually. In several subjects, we could not distinguish subcomponents

of the MRCP due to a poor signal-to-noise ratio. In addition, some patients showed a different time course of negativity at around the time of the movement onset (corresponding to the NS' component) between the two tasks. Therefore, to simplify the interpretation of the results and to exclude the experimenter's bias, we measured the amplitude of MRCPs just at the movement onset from the baseline in all subjects, and in the Results we call this pre-movement potential shift the BP. Thus, this represents an overall cerebral activity of the preparatory/executive process for movement. In addition, to investigate the post-movement cerebral processing of each movement, the peak time of MRCP immediately after the movement onset (motor potential; MP) and its amplitude from the baseline were measured at the electrode where the negativity was maximal (C1 or Cz) for each subject. Actually, the MP amplitude was obtained by subtracting the BP amplitude measured at the movement onset from the amplitude measured at the peak time of MP. For control, the data from normal subjects (Terada *et al.*, 1995) were re-analysed by using exactly the same method as used for the present patient group. Afterwards, statistical analysis was done in each group by using analysis of variance (ANOVA) with repeated measures design with two factors [electrode position (Electrode) and task effect (Task)]. Within each group, a paired *t*-test was applied to compare the BP amplitudes at each electrode between the two tasks.

In order to compare the distribution of BP between the two tasks for each group by cancelling out the effect of absolute amplitude difference, the data were normalized by dividing the values measured at all electrodes by the maximal BP amplitude for each task for each individual subject. Then, repeated measures mixed type ANOVA was adopted with three factors [within-group factors: Electrode and Task, between-group factor: effect of disease (Disease)]. To investigate the horizontal distribution of BP over the central area, the above procedure was applied to five selected central electrodes (C3, C1, Cz, C2 and C4). In order to compare the normalized BP amplitude at each electrode between the two groups, separate one-way ANOVA was adopted for each task. The significance of degrees of freedom for all repeated measure analysis was evaluated by using Greenhouse–Geisser correction.

Results

On task performance, all the patients with focal hand dystonia studied here reported that the contraction task was more difficult to perform than the relaxation task. This was opposite to the situation in the normal controls; they found the relaxation task more difficult than the contraction (Terada *et al.*, 1995).

Muscle relaxation versus contraction in focal dystonia

In the patient group, there was no difference in the BP onset time between the two tasks [$F(1,7) = 4.67$, $P = 0.67$]

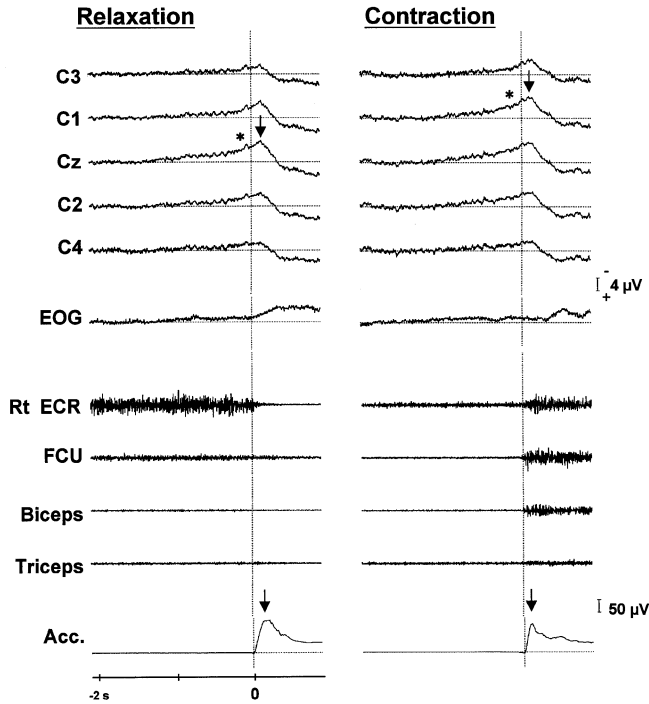


Fig. 2 Grand average waveforms of BP and surface EMG activities for the two motor tasks in the focal hand dystonia group. In the relaxation task (total number of sweeps: 644), the negative BP starts at ~1.5 s prior to the movement onset. It is maximal at Cz (asterisk) and symmetrically distributed throughout the pre-movement period. In the contraction task (total number of sweeps: 520), the BP starts at ~1.4 s prior to the movement onset, and is maximal at C1 at the movement onset (asterisk). The post-movement MP peak (arrows) is maximal at Cz in the relaxation task, whereas it is maximal at C1 in the contraction, and is equal in time after the movement onset in the two tasks. Acc. = accelerogram; ECR = extensor carpi radialis muscle; FCU = flexor carpi ulnaris muscle; EOG = electrooculograph; Rt = right.

Table 1 Onset time of BP for the muscle relaxation and contraction tasks in the two groups

	Relaxation (ms, mean \pm SD)	Contraction (ms, mean \pm SD)
Focal dystonia	-1497.0 \pm 89.4	-1387 \pm 196.9
Normal control	-1521.0 \pm 233.6	-1216.8 \pm 334.7

‘-’ indicates before movement onset.

(Table 1). The amplitude of BP in the contraction task was maximal at the left central area (C1) ($6.22 \pm 3.31 \mu\text{V}$) and predominantly distributed over the left hemisphere (Figs 2 and 3). In the relaxation task, the BP was maximal at the midline central area (Cz) ($4.37 \pm 1.71 \mu\text{V}$) and was almost symmetrically distributed (Figs 2 and 3). The BP appeared larger on the right hemisphere in the frontal and parietal areas, but the difference did not reach statistical significance (Fig. 3). Individually, seven out of eight subjects showed the C1 maximum in the contraction task, whereas the remaining subject showed the maximal amplitude at Cz. In the relaxation

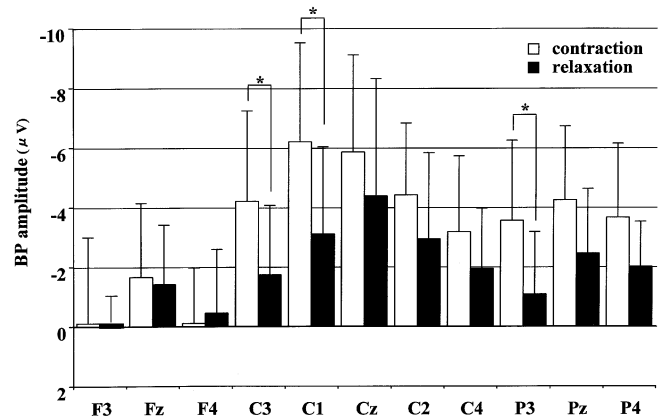


Fig. 3 Distribution of BP amplitude at the movement onset for the muscle contraction and relaxation tasks in the focal hand dystonia group. The BP is distributed predominantly over the central area in both tasks, but the horizontal distribution is different between the two tasks. In the contraction task, the BP is maximal at C1, and distributed predominantly over the left hemisphere (contralateral to the movement). In the relaxation task, the BP is maximal at Cz and almost symmetrically distributed. The difference reached the significance level at C1, C3 and P3 ($P < 0.05$, paired t test).

Table 2 Peak time of MP for the muscle relaxation and contraction tasks in the two groups

	Relaxation (ms, mean \pm SD)	Contraction (ms, mean \pm SD)
Focal dystonia	+112.1 \pm 61.8	+107.3 \pm 42.0
Normal control	+225.8 \pm 68.4	+126.1 \pm 31.1

‘+’ indicates after movement onset.

task, the BP was maximal at Cz in all subjects. ANOVA did not disclose a main effect of Task [$F(1,7) = 4.76$, $\epsilon = 1.00$, $P = 0.07$], but significant interactions between the two factors were present [Task \times Electrode: $F(10,70) = 3.60$, $\epsilon = 0.22$, $P < 0.05$]. Significant amplitude difference was observed at the left central (C1 and C3) and the left parietal (P3) region ($P < 0.05$, paired t -test); the BP amplitudes at those electrodes were lower in the relaxation task than in the contraction task (Fig. 3). Therefore, the interaction can be explained by the amplitude diminution over the left hemisphere in the relaxation task.

The MP peak time showed no significant difference between the two tasks ($P = 0.76$, paired t -test) (Table 2). The MP amplitude was maximal at C1 ($-2.38 \pm 0.95 \mu\text{V}$) in the contraction task and at Cz ($-3.73 \pm 2.72 \mu\text{V}$) in the relaxation task. In both tasks, it was distributed predominantly over the frontocentral area. ANOVA disclosed neither Task effect [$F(1,7) = 1.29$, $\epsilon = 1.00$, $P = 0.29$] nor Electrode interaction [$F(10,70) = 1.53$, $\epsilon = 0.25$, $P = 0.24$] for the MP amplitude, suggesting that the MP in focal hand dystonia was not affected by the task in terms of peak time, amplitude and potential distribution.

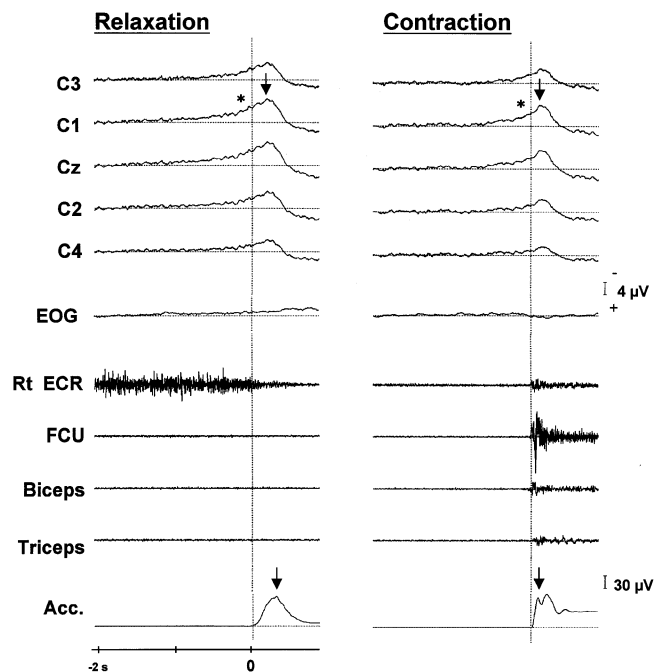


Fig. 4 Grand average waveforms of the BP and surface EMG activities for the two motor tasks in the normal control group. In both the relaxation and contraction tasks, the BP starts at ~ 1.6 s prior to the movement onset with symmetric distribution, and it becomes maximal at C1 just at the movement onset (arrows). Total number of sweeps: 783 for the relaxation and 893 for the contraction task. The waveforms of the BP in the control group were rearranged from those shown in Fig. 5 of the paper by the authors' group (Terada *et al.*, 1995) with permission. The post-movement MP peak occurs earlier after the movement onset in the contraction task than in the relaxation task. Acc. = accelerogram; ECR = extensor carpi radialis muscle; FCU = flexor carpi ulnaris muscle; EOG = electrooculograph; Rt = right.

Muscle relaxation versus contraction in the control group

In the normal control group, BP started symmetrically and became maximal at C1 just before the movement onset in both tasks ($3.63 \pm 1.66 \mu\text{V}$ in the contraction and $4.37 \pm 1.71 \mu\text{V}$ in the relaxation) (Fig. 4). As reported previously, there was a significant difference in the onset latency of BP between the two tasks [$F(1,9) = 11.99$, $P < 0.01$; Table 1]. As for the individual analysis, in the contraction task, five out of the 10 subjects showed the C1 maximum, three Cz and the remaining two C3. In the relaxation task, half of the subjects showed the C1 maximum, four Cz and one C3.

In comparing the two tasks within the normal control group, there was no Task effect [$F(1,9) = 1.53$, $\epsilon = 1.0$, $P = 0.25$], but there was a significant interaction between the two factors [Task \times Electrode: $F(10,90) = 4.12$, $\epsilon = 0.39$, $P < 0.01$]. This interaction was caused by the general increase of BP amplitude (especially in the parietal area) in the relaxation task, but only P3 showed a significant difference ($P < 0.05$, paired t test).

The MP peak time was significantly earlier with respect

to the movement onset in the contraction task than in the relaxation task ($P < 0.01$, paired t test) (Table 2). The MP amplitude was maximal at C1 in both tasks (contraction, $-3.15 \pm 1.61 \mu\text{V}$; relaxation, $-3.56 \pm 2.84 \mu\text{V}$) with predominantly frontocentral distribution. ANOVA disclosed neither Task effect [$F(1,9) = 0.41$, $\epsilon = 1.00$, $P = 0.54$] nor Electrode interaction [$F(10,90) = 0.34$, $\epsilon = 0.19$, $P = 0.76$] for the MP amplitude.

Focal dystonia versus control

There was no significant difference in the onset time of BP between the two groups for either task [relaxation: $F(1,16) = 0.08$, $P = 0.79$, contraction: $F(1,16) = 1.61$, $P = 0.22$] (Table 1). When comparing the amplitude values of BP at all electrodes, ANOVA with three factors disclosed only a main effect of the Electrode [$F(10,160) = 18.89$, $\epsilon = 0.22$, $P < 0.001$], and this effect was not affected by Disease [$F(10,160) = 2.89$, $\epsilon = 0.22$, $P < 0.19$]. The interaction of the factors (Task \times Electrode \times Disease) was not significant [$F(10,160) = 2.07$, $\epsilon = 0.35$, $P = 0.07$].

ANOVA at the five central channels showed significant interaction of the factors [Task \times Electrode \times Disease: $F(4, 4) = 4.42$, $\epsilon = 0.61$, $P < 0.05$]. This indicates that the normalized BP distribution at the central area was significantly influenced by the two factors (Task and Disease).

A separate ANOVA comparing the normalized amplitude values at each electrode in the two groups for each task disclosed the significant difference at C1 and C3 in the relaxation task; they were smaller in the patient group than in the control group (Fig. 5). In the contraction task, however, the differences appeared at C2 and C4 (the central area ipsilateral to the movement), and the normalized amplitude at those electrodes was larger in the patient group than in the normal controls (Fig. 5).

The MP peak time was significantly affected by Disease [$F(1,16) = 8.39$, $P < 0.02$]. The difference between the groups was found only in the relaxation task, i.e. the MP peak time in the relaxation task in focal hand dystonia was significantly earlier with respect to the movement onset than that in controls (Table 2). However, the MP amplitude and scalp distribution were not influenced by Disease [Task \times Electrode \times Disease: $F(10,160) = 1.22$, $P = 0.31$].

Discussion

This study was aimed mainly at elucidating how the cortical mechanism underlying the preparation for voluntary hand muscle relaxation was affected in focal hand dystonia. The main finding was a diminished amplitude of the slow pre-movement shift (BP) preceding voluntary relaxation of the right (affected) hand muscle over the left central area in the patients. In the study of normal subjects employing exactly the same methods, the authors' group previously reported that the slow potentials preceding voluntary, self-paced relaxation and contraction of the right hand muscle were

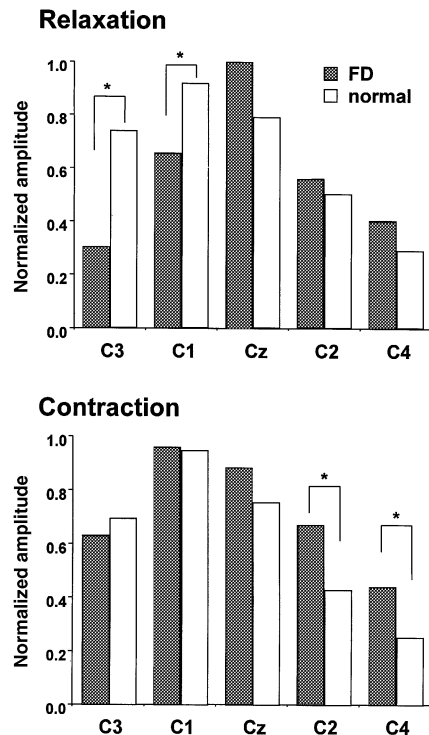


Fig. 5 Normalized distribution of BP amplitude at the central area for each task, comparing the two groups. In the relaxation task, the normalized BP amplitude in the left hemisphere is significantly diminished in the patient group (FD) compared with the controls (asterisks, C3 and C1, $P < 0.05$, separate ANOVA). In the contraction task, however, the differences are seen at C2 and C4 (asterisks) where it is larger in the patient group than in the normal control ($P < 0.05$, separate ANOVA).

quite similar to each other in terms of the waveform and scalp distribution (Terada *et al.*, 1995). Taking into account the results of subdural recording of MRCPs associated with muscle contraction in epilepsy patients, which suggested the SI-MI and SMA as the main generator sources (Neshige *et al.*, 1988; Ikeda *et al.*, 1992), it was postulated that the potential preceding the muscle relaxation might represent excitatory postsynaptic potentials of either corticospinal neurons projecting to the spinal inhibitory neuron or inhibitory interneurons in the SI-MI and/or SMA (Terada *et al.*, 1995). If this assumption is correct, the smaller BP at the contralateral central area in the relaxation task compared with the contraction task might suggest the impaired activation of these inhibitory motor systems in the contralateral SI-MI in focal hand dystonia patients. An abnormality of the cortical inhibitory motor system in focal hand dystonia was reported by using TMS applied to the motor cortex; the motor evoked potential was less inhibited by a conditioning stimulus of subthreshold intensity in focal hand dystonia compared with normal controls, although there was no difference in the threshold of motor evoked potential at rest between focal hand dystonia and the controls (Ridding *et al.*, 1995).

The presence of a cortical inhibitory system projecting to the spinal motor neuron was demonstrated in primates by Schmidt and McIntosh (Schmidt and McIntosh, 1990). They

explored the neuronal function in the precentral gyrus in monkeys by using intracortical microstimulation. By giving trains of microstimuli to cells in the precentral gyrus, abrupt inhibition or contraction of the forearm muscle was elicited, as in the TMS study in human, and such inhibitory cells were scattered among the excitatory cells in the precentral gyrus. An inhibitory effect of the stimuli on such cells was observed similarly during voluntary movement and during muscle activation caused by vibration. It suggested the possibility that the motor cortex might contain a neuronal population which caused spinal presynaptic inhibition by activating inhibitory interneurons in the spinal cord (Schmidt and McIntosh, 1990). Moreover, they found that in certain regions just adjacent to the area showing inhibition, the microstimulation caused an excitation in both extensor and flexor muscles (co-contraction). In other regions, the stimuli produced excitation of one extensor muscle and inhibition of another extensor muscle, or excitation of a flexor muscle and simultaneous inhibition of another flexor muscle. If such inhibitory cells are functionally impaired in humans, presumably as the result of the deficient control from basal ganglia, a dystonic symptom might occur, and an abnormal MRCP as shown in the present study might reflect the impaired function of the inhibitory motor preparatory systems.

Previous MRCP studies employing muscle contraction in various dystonic patients also disclosed an abnormal distribution of BP, i.e. a diminished amplitude of the pre-movement potential over the central area contralateral to the movement (Fève *et al.*, 1994; Deuschl *et al.*, 1995; Van der Kamp *et al.*, 1995). However, we did not observe such specific diminution of BP in the patients with focal hand dystonia, at least preceding the voluntary muscle contraction task (Figs 2 and 3). In fact, both the focal hand dystonia and control groups showed the maximal amplitude of BP at the contralateral central area in the contraction task and, in the ipsilateral central area, the normalized amplitude of BP was even larger in focal hand dystonia than in the controls. The absence of laterality can be interpreted as a loss of dominance which is normally seen in unilateral movement, and it suggests a functional impairment of the contralateral SI-MI in focal hand dystonia. It is in good agreement with the results of previous studies (Fève *et al.*, 1994; Deuschl *et al.*, 1995; Van der Kamp *et al.*, 1995). First, the different degree of effort needed to perform the contraction task in the present focal hand dystonia group and in the reported patients should be taken into account to explain the differences. All the previous studies employed easy, phasic, brisk movements of the finger or wrist, whereas our contraction task required the patients to keep the flexed wrist position for as long as 5 s. In fact, some patients could not control the magnitude of wrist flexion to an appropriate level, i.e. they tended to make an excessive contraction compared with normal controls. It has been shown that when a complex task is employed, the BP loses its contralateral dominance just before the movement onset, probably because the SI-MI becomes active bilaterally as the complexity increases (Benecke *et al.*, 1985; Simonetta

et al., 1991; Kitamura *et al.*, 1993; Shibasaki *et al.*, 1993). Therefore, the great effort made by the patients in the present contraction task might have obscured the abnormality of the absolute BP amplitude that was found in the previous studies.

Furthermore, the analysis method employed in the present study was different from that used in the previous ones. Those previous studies selectively measured a subcomponent of pre-movement potentials (NS') which appears immediately before the movement onset, but we analysed the whole pre-movement activity measured from the baseline at the movement onset. In the present study, the waveform of the NS' component for each task varied among the patients, probably due to a smaller number of acceptable trials (poor signal-to-noise ratio). Therefore, in order to avoid any arbitrary subdivision of BP into NS1 and NS2, we used the amplitude of MRCP measured at the movement onset as an indicator of movement preparation and/or execution. It may be another cause which masks any significant difference in the present results of the contraction task between the two groups.

The neostriatum, especially the putamen, is regarded as the structure responsible for dystonia (Fross *et al.*, 1987; Lorenzana *et al.*, 1992; Hallett, 1993). Hallett proposed that the involuntary movement in dystonia could be explained by overactivity of the direct pathway via the globus pallidus pars interna/substantia nigra pars reticulata (Hallett, 1993). However, based on the studies of Parkinson's disease, the question as to whether the BP is affected by basal ganglia disorder or not still remains unsolved (Deecke *et al.*, 1977; Barrett *et al.*, 1986; Dick *et al.*, 1989; Ikeda *et al.*, 1997). In contrast to Parkinson's disease, the results of the studies of BP in focal hand dystonia seem consistent among the few different studies reported so far (Fève *et al.*, 1994; Deuschl *et al.*, 1995; Van der Kamp *et al.*, 1995). Although the interaction of the SMA/SI-MI and basal ganglia in the generation of BP is still unclear, the generating mechanism of BP in the two basal ganglia disorders, Parkinson's disease and focal hand dystonia, seems to be different. In patients with Parkinson's disease, a PET activation study using H₂¹⁵O showed poor activation in the SMA and dorsolateral prefrontal cortex, but activation in the SI-MI was preserved, and was as much as in the normal controls (Playford *et al.*, 1992; Brooks, 1997; Samuel *et al.*, 1997). In contrast, activation in both the caudal part of the SMA and the SI-MI was diminished in patients with focal hand dystonia (Tempel and Perlmutter 1993; Ceballos-Baumann *et al.*, 1995). These findings suggest that inconsistent results of MRCP in Parkinson's disease may be due, at least partly, to the relatively preserved activity of the SI-MI in the patients with Parkinson's disease. Thus, the present results in focal hand dystonia are consistent with those of the previous MRCP and PET studies, and we postulate that basal ganglia function can influence the findings of MRCP in different ways in Parkinson's disease and focal hand dystonia. According to a recent hypothesis, basal ganglia do not necessarily generate movements, but they act broadly to inhibit the competing

motor mechanisms that would otherwise interfere with the desired movement (see review by Mink, 1996). A PET study showed a decreased dopaminergic activity in the putamen in patients with focal dystonia (Perlmutter *et al.*, 1991, 1997a). Furthermore, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated baboons showed transient unilateral dystonic symptoms followed by permanent parkinsonism (Perlmutter *et al.*, 1997b). Perlmutter *et al.* suggested that in patients with dystonia, the impaired striatal D2 activity may cause diminished activity of an indirect pathway of the basal ganglia and subsequent disfacilitation of thalamocortical projections to the MI and SMA (Perlmutter *et al.*, 1997b).

One of the clinical characteristics of focal hand dystonia is task-specificity. Byl *et al.* reported a primate model of focal dystonia, in which a rapid, repetitive, daily behavioural hand movement task caused remapping of the somatotopic representation of the somatosensory cortex (Byl *et al.*, 1996). Based on neurophysiological evidence, including abnormal responses to a peripheral vibratory stimulus (Tempel and Perlmutter 1990, 1993; Kaji *et al.*, 1995b), the possibility of abnormal sensory processing in patients with dystonia was proposed (Hallett, 1995). In the paradigm employed in the present study, the relaxation always had to be preceded by muscle contraction. Therefore, this condition might have some effect similar to vibration on the sensory cortex, by means of activation of muscle afferent pathways. If that is the case, it is reasonable to postulate that the abnormal sensory processing in dystonia is partly responsible for impaired MRCP in our relaxation paradigm. Since the recording of MRCPs requires the cooperation of the subject for an extended period, the present study in the patient group did not take the task-specificity into account. Further study aimed at the elucidation of this mechanism is warranted.

In the present study, we also examined the post-movement activity. We found a different MP peak time in the two groups in the relaxation task. The MP determined at the central electrodes in the present study seems to be closely related to the frontal peak of MP reported in the previous study in terms of its peak time (Terada *et al.*, 1995). The previous study explained, based on the findings of the accelerograms, that the different peak time of the fpMP in the two tasks in normal subjects was probably caused by jittering of the relaxing speed of the hand muscles. This might also hold true for the comparison between focal hand dystonia and controls in the present study. As shown in Figs 2 and 4, the accelerograms in the relaxation task showed a lesser degree of jittering in the focal hand dystonia group compared with the control group. In addition, the peak time of the MP seems to be very close to the peak of the accelerogram. Post-movement activities of the MRCP seem to reflect kinaesthetic input from the peripheral nervous system (Tarkka and Hallett, 1991), and subdural recording of the MRCP showed that a major post-movement component was generated in the primary somatosensory cortex (Ikeda *et al.*, 1995). It is postulated further that the post-movement sensory processing in the relaxation task in focal hand

dystonia is different from that in controls, as recently suggested (Hallett, 1995). The delayed peak time of MPs in the relaxation task might suggest that the post-movement cerebral processing in this condition might require more steps compared with the contraction task. However, it is difficult to reach any conclusion in this regard based only on the present results, and further studies are warranted to unravel this particular issue.

Acknowledgements

The authors wish to thank Miss N. Samura for technical assistance in data acquisition. This study was partly supported by Grants-in-Aid for Scientific Research (A) 09308031, (A) 08670705 and (C) 10670583, and on Priority Areas 08279106 from the Japan Ministry of Education, Science, Sports and Culture, and a Research Grant for the Future Program JSPS-RFTF97L00201 from the Japan Society for the Promotion of Science.

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Received February 1, 1999. Accepted March 2, 1999