Abnormal premovement gating of somatosensory input in writer’s cramp

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Summary
One characteristic of focal dystonia is the sensory trick, by which sensory input to a certain area of the body can reduce abnormal contractions in muscles nearby. This suggests that adjusting the link between sensory input and movement allows motor commands to be issued more effectively from the brain. To explore this sensorimotor link, we studied the attenuation (gating) of somatosensory evoked potentials (SEPs) before and during hand movements in patients with writer’s cramp. For premovement gating, 10 patients and 11 age-matched normal subjects were given a warning sound followed 1 s later by an electric stimulus to the right median nerve at the wrist. The latter served both as a reaction signal to start a finger extension task and as the input to evoke SEPs over the scalp. Because reaction times always exceeded 70 ms, short-latency SEPs thus obtained were unaffected by the afferents activated by the movement. The amplitudes of frontal N30 components were significantly decreased over the frontal leads compared with SEPs elicited at rest (P < 0.002) in the normal group, whereas significant gating was found not for N30 but for frontal P22 (P = 0.002) in the patient group. For midmovement gating studies, SEPs to the right median nerve stimulation were recorded in 16 patients and 12 age-matched normal subjects at rest, and during active and passive finger extension-flexion movements. In contrast to the premovement SEPs, the frontal N30 was equally gated during active and passive movements both in the patient (P ≤ 0.002) and the normal group (P ≤ 0.003). These findings indicate that in writer’s cramp the sensitivity of sensory input channels from the hand is wrongly set by the central command to move. Perhaps the sensory trick, by supplying additional input not usually present during unobstructed movement, is a manoeuvre to correct this imbalance. Dystonia may result not only from abnormalities in the central motor command but also from disturbed central processing of sensory input.

Keywords: writer’s cramp; dystonia; motor subroutine; somatosensory evoked potential; premovement gating

Abbreviations: ANOVA = analysis of variance; CNV = contingent negative variation; EOG = electro-oculogram; SEP = somatosensory evoked potential

Introduction
Writer’s cramp is increasingly recognized as a task-specific form of focal dystonia (Sheehy and Marsden, 1982). In the early stage, it usually affects only writing (simple writer’s cramp), although later symptoms may involve other tasks (dystonic writer’s cramp). This task-specific disorder provides a unique opportunity to explore the physiological mechanisms involved in performing a specific motor task.

The movements of patients with writer’s cramp are characterized by co-contraction of agonist and antagonist muscles and the overflow phenomenon, in which inappropriate muscles are recruited for writing (Rothwell et al., 1983; Berardelli et al., 1998). During movement execution, one or more different EMG patterns (long spasms, repetitive or sometimes rhythmic bursts, and irregular brief jerks) may occur (Yanagisawa and Goto, 1971; Berardelli et al., 1998). These patterns of muscle contraction are relatively constant within a subject, and represent a specific abnormality in the motor strategy.

Dystonic movements are typically aggravated by an attempt to perform an action (Oppenheim, 1911). Clinical symptoms of writer’s cramp often become manifest upon holding a pen, even before writing (Sheehy and Marsden, 1982). Furthermore, just the intention to write can trigger dystonic spasms in some patients. These clinical observations indicate that an abnormal motor strategy may already be set up during the premovement phase. In fact, abnormalities in the cortical...
potentials preceding the movement such as contingent negative variation (CNV) (Kaji et al., 1995a; Ikeda et al., 1996; Hamano et al., 1999) and movement-related cortical potentials (MRCPs) (Deuschl et al., 1995; Van der Kamp et al., 1995) have been reported.

In addition to these task-specific symptoms, sensory input has a major role in the pathophysiology of dystonia (Hallett, 1995); dystonic spasms are reproduced by stimulating muscle afferents as in tonic vibration reflex, and are abolished by muscle afferent blocks (Kaji et al., 1995b). The sensory trick, an important characteristic of dystonia, is also seen in writer’s cramp; touching a part of the writing hand with the other hand may be effective in improving abnormal spasms (Sheehy and Marsden, 1982). Indeed, dystonia may be regarded as a disorder in matching sensory input for motor output (Lenz et al., 1999).

The present study was undertaken to investigate the relationship between sensory input and motor strategy in focal dystonia by analysing the attenuation of somatosensory evoked potentials (SEPs) before and during a movement (gating) (Rushton et al., 1981; Jones et al., 1989). Gating of SEPs during movement can be caused by the competition between the sensory stimuli and the afferents activated by the movement itself (peripheral gating). It may also be caused by the central command to move (central gating).

In this study, we used a method that allows us to distinguish central from peripheral gating of SEPs using a reaction time paradigm in which subjects were given a warning sound followed 1 s later by an electric shock to the right median nerve at the wrist (Shimazu et al., 1999). The latter served both as a reaction signal to start a nerve at the wrist (Shimazu followed 1 s later by an electric shock to the right median nerve). Some patients had been taking baclofen, previously received treatment in muscles innervated by the segment of SEPs evoked within the first 50 ms after the stimulus could not be affected by peripheral gating because the actual movement began at least 70 ms after the sensory stimulation (premovement gating). Romo and colleagues have demonstrated in the monkey that the sensory input is conveyed to the supplementary motor area only when it controls movement (Romo et al., 1993). Therefore, this method may be suited to analysing any sensory input to the motor cortices, because the stimulus for recording SEPs cues the movement. We also examined how the SEPs were attenuated during movement (midmovement gating), a process which involves both peripheral and central gating (Jones et al., 1989).

The results were consistent with the hypothesis that dystonia is associated with abnormalities in a preconceived motor program, or subroutine, which defines the strategy for performing a movement in relation to the sensory input (Kaji et al., 1995c).

**Methods**

**Subjects**

For premovement gating, 11 patients with writer’s cramp (Patients 1–11; nine men and two women; mean age 48.9 years, range 23–69 years) were studied (Table 1). The mean disease duration was 3.4 years. One of these patients (Patient 11) also underwent topographic mapping of SEPs over the scalp. Eleven age-matched normal volunteers (five men and six women; mean age, 49.9 years, range 28–63 years) were studied as the control group. They were in good health and free from any neurological diseases.

For midmovement gating, another group of 16 patients with writer’s cramp (Patient 12–27; 14 men, two women; mean age 40.4 years, range 20–64 years; mean disease duration 3.3 years; Table 1) was compared with 12 age-matched normal control subjects (10 men, two women; mean age 37.7 years, range 25–64 years). Although different patients were tested for each gating study, both patient groups were similar in age, sex, disease duration and task-specificity (Table 1). All the patients and normal subjects were right-handed.

All of these patients were able to relax their muscles completely, and no dystonic movements or contractions were found at rest. The diagnosis of writer’s cramp was based on characteristic clinical features: difficulties in writing caused by abnormal muscle contractions or abnormal posturing with preserved muscle strength (Sheehy and Marsden, 1982). All the patients had their symptoms exclusively in the right hand. Although about half of the patients studied were classified as ‘dystonic’, they were able to write a few lines and to perform normally the brisk finger extension or extension–flexion movements adopted in our experimental paradigms.

They had no family history of dystonia or other movement disorders and had not received muscle afferent blocks (Kaji et al., 1995b) for more than 1 month, or had botulism toxin treatment for more than 1 year, so they were not expected to have severe damage to the muscle (Hassan et al., 1995). The histories for these treatments were similar in the patients for the premovement gating studies and in those for midmovement gating studies. None of the patients had previously received treatment in muscles innervated by the median nerve. Some patients had been taking baclofen, etizolam and/or clonazepam, which were discontinued at least 24 h prior to the study.

They were seated in a comfortable armchair with hands relaxed on the armrest of the chair and their eyes fixated on a mark placed 1 m in front of them. The recording room was sound-attenuated, electrically shielded and air-conditioned to a temperature of 25–28°C. All subjects gave their informed consent for participation in this study. These studies were approved by the Ethics Committee of Kyoto University School of Medicine.

**Experimental procedure**

**Premovement gating**

The method for premovement gating has been reported elsewhere (Shimazu et al., 1999), and thus is described here only briefly. Subjects were given a pair of warning (S1) and
Table 1 Clinical profile of patients with writer’s cramp investigated in the present study

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Task specificity*</th>
<th>Duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/M</td>
<td>Dystonic</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
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<td>Dystonic</td>
<td>4</td>
</tr>
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</tr>
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<tr>
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<td>6</td>
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<td>Dystonic</td>
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Mean (years) 48.9  3.4

*Simple or dystonic writers cramp (task specificity) was based on the classification of Sheehy and Marsden (1982).
Fig. 1 Experimental design for the premovement gating study (A) and the results of a control experiment to test CNV contamination (B). A click sound (S1: ‘Ready’ signal) was followed by an electric shock (S2: ‘Go’ signal) applied to the wrist 1 s later. Three conditions (rest, premovement and count gating) were tested in turn. A control experiment to examine the effect of the high-pass filter on CNVs was performed in a 43-year-old normal man. Increasing the low frequency cut-off of the high-pass filter from 0.05 to 1.5 eliminated all the CNVs during the period of 0–50 ms after S2 (arrow). To exclude SEPs, LED stimulus was used as S2 in this experiment. The rest of the method was the same as in the main study. The upper two traces show the superimposition of the waveforms from nine electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with the bandpass filter of 0.05–100 Hz (upper) and 1.5–100 Hz (lower). The bottom two traces show EOG and rectified surface EMG activities recorded with the same bandpass filter as in the premovement gating study.

(a) Premovement gating

Trials associated with background EMGs larger than 50 µV within 70 ms after S2, or those exceeding 5 µV in the EOG channel were excluded manually from averaging. The total number of sweeps per average was always kept over 100.

Because the task inevitably produced a CNV that could contaminate the SEP data, we conducted a control study to compare the averaged EEGs as described above using the same high-pass filter setting as used for SEPs (1.5–100 Hz) with those recorded with the filter setting conventionally used for recording CNV (0.05–100 Hz) (Fig. 1B). In this particular experiment, we used a light emitting diode stimulus as S2 instead of electric shock. As a result, the high-pass filter setting employed in the present study eliminated all CNV components at least for the period analysed (0–50 ms after S2).

(b) Midmovement gating

SEPs for midmovement gating were recorded with a standard EMG machine (Viking II; Nicolet Biomedical, Madison, Wis., USA). Percutaneous electric stimulus (0.2 ms duration) was applied to the right median nerve at the wrist using a regular rate of 2.9 Hz. The stimulus intensity was adjusted to 20% above the motor threshold. EEG recordings were made from Fp1, Fp2, F3, F4, C3, C4 and P3 using surface electrodes, with linked earlobes serving as the reference. The analysis time was 100 ms after the stimulus. The mixed nerve volley was concurrently monitored at the elbow ipsilateral to the stimulation with a pair of surface electrodes placed 3 cm apart along the nerve trunk. The bandpass filter used was 10–1000 Hz. One thousand sweeps were averaged alternately to obtain two averages of 500 sweeps each, to assure reproducibility. We could not use the same stimulus rate as in the premovement gating study because the length of time required to obtain reproducible averages would be hardly tolerable for the patients. Neither could we use the same filter settings because of the higher artefact level during the movement than in the premovement period.

Proximal and distal interphalangeal joints were fixed with a splint so that only the metacarpophalangeal joint could be moved. SEPs were recorded at rest, and during active and passive movements in a single session. The subjects were instructed to flex and extend the metacarpophalangeal joints from the horizontal position to 45° below, which was repeated at a self-paced rate of about 1 Hz, irrespective of the timing of median nerve stimulation. Passive movements were produced by an experimenter so as to mimic the active movement.

Data analysis

We made measurements on the following SEP components: P14 far field, P22, N30a and N30b (this separation was seen only in the premovement study) at frontal electrodes, and N20, P26 and N34 at central and parietal electrodes (Mauguière et al., 1983; Desmedt et al., 1987; Garcia Larrea et al., 1992; Fujii et al., 1994).

For identification of the peaks, we used the following criteria. P14 far field component was seen at 10–16 ms of latency in contralateral and central leads in all subjects. In ipsilateral leads, the largest positivity in the same latency range was measured as P14, if the peak was poorly identified. The same principle of using the time point with largest negative or positive deflections in the specified time range as the component latency applies to the other components
whenever the peak was not well formed. We defined frontal P22 as the first positive peak following P14 at 15–25 ms in frontal leads. N30a was the negative peak formed between 23–33 ms, immediately following P22 at frontal leads. The second negative peak during this time range at frontal leads was named N30b (Fujii et al., 1994). We measured N20 as the first negative peak between 14 and 22 ms, and P26 as the first positive peak between 22 and 30 ms following P14 at central and parietal leads. We defined N34 as the first negative peak between 22 and 40 ms after P26 at central and parietal leads. Despite the term, N30b sometimes had longer latency than that of N34, and N34 was not always seen. N30a was found in all subjects, whereas N30b was present in all patients but in only nine out of 11 normal subjects.

The amplitudes of SEP peaks were calculated from the baseline, which was defined as the average potential between 4.0 and 6.0 ms after stimulation of the median nerve. Before making grand averages of traces from all subjects, we aligned all P14 and P30 far field waveforms to a latency of 15 ms in order to compensate for differences in peripheral conduction times (Garcia Larrea et al., 1992).

Data from the premovement and midmovement gating tasks were analysed separately. Three-way analysis of variance (ANOVA) with repeated measures design was performed on the data using the following three factors: group (patients versus controls), task (rest versus movement versus count the number of S2 stimuli), and scalp site or SEP component. The amplitude of each SEP component was analysed independently at different scalp sites (scalp site), and, except for N34, was later represented as the average potential between each SEP component measured at a representative scalp site [component (electrode): N20 (P3), P22 (F3), P26 (C3), N30a (F3) and N30b (F3)]. Only N34 component was later represented as the average potential between each SEP component measured at a representative scalp site [component (electrode): N20 (P3), P22 (F3), P26 (C3), N30a (F3) and N30b (F3)]. Only N34 component was analysed separately at Cz and Pz [N34 (Cz) and N34 (Pz)].

Further analysis concentrated on six SEP components (N20, P22, P26, N30a, N30b and N34) that could be identified at more than one scalp site (e.g. N20 at C3 and P3). In order to test whether each SEP component behaved similarly at each scalp site we first performed a separate three-way ANOVA for each SEP component with group, task and scalp site as main factors. In no case was there a significant effect of scalp site as a main factor or as an interaction term except for the N34 component [as a main factor: \(F(1,15) = 13.95, P = 0.002\) and as an interaction of scalp site \(\times\) task: \(F(1,15) = 3.62, P = 0.039\)]. This means that, apart from N34, each SEP component at different locations behaved similarly, although a single component does not necessarily have an independent or a single generator. Because of this we conducted the remainder of the analysis on the amplitude of each SEP component measured at a representative scalp site [component (electrode): N20 (P3), P22 (F3), P26 (C3), N30a (F3) and N30b (F3)]. Only N34 component was included among these conditions, although the present study was not designed for its quantitative assessment.

The initial three-way ANOVA included all three tasks, all seven SEP components [N20 (P3), P22 (F3), P26 (C3), N30a (F3), N30b(F3), N34 (Cz) and N34 (Pz)] and both groups of subjects. The results (Table 2) revealed that there was a significant main effect of SEP component and task. Group was not significant. Significant interactions were seen for group \(\times\) component, task \(\times\) component and group \(\times\) task \(\times\) component.

Separate three-way analyses were performed comparing rest versus count, and rest versus movement. There were no significant main or interaction effects in the rest versus count comparison, indicating that the SEPs were unaffected by the attentional demands of counting the number of S2 stimuli. Therefore, we have concentrated in the remainder of the results on the comparison between rest and movement.

Table 3 shows the interaction between group \(\times\) task separately for each SEP component: a significant two-way group \(\times\) task interaction occurred for only three SEP components, P22, N30a and N30b. This was due to the fact that (see Table 4): (i) N30a and N30b were suppressed by movement in control subjects but not in the patients (Figs 2, 4 and 8); and (ii) P22 was suppressed by movement in the

**Results**

**Premovement gating**

The premovement gating study compared SEP sizes between patients and controls in three different conditions: (i) rest, (ii) moving the hand in response to S2 and (iii) counting the number of S2 stimuli. Figures 2 and 3 show the grand average evoked potentials from control and patient groups; superimposed individual traces from each subject are plotted in Figs 4 and 5. Although the shape of the baseline SEP was similar in both groups, the SEP of control subjects was smaller than at rest in the premovement condition, whilst it was unaffected or enhanced in the patient group. Qualitatively, it appeared that the differences between groups were most evident on the frontal P22 and N30 components of the potential. The counting condition had no effect on the SEP in either group. Neither patients nor normal subjects reported any difference in the perceived strength of the electrical stimuli (S2) among these conditions, although the present study was not designed for its quantitative assessment.
Fig. 2 Grand averaged waveforms of SEPs following the right median nerve stimulation in the normal group (n = 11 in the ‘Rest/Premovement’ task and n = 9 in the ‘Rest/Count’ task). Data from representative electrodes Fz, F3, C3 and P3, and the rectified EMG are shown. The thin lines represent waveforms at rest and the thick lines show those at tasks (premovement condition in the left column and counting task in the right column). The asterisks indicate the SEP components showing significant amplitude differences (*P < 0.05, **P < 0.01) analysed by paired t-test. The mean reaction time measured from S2 to the rectified EMG onset was 85.8 ms. The gating is seen in the frontal N30 components (N30a, N30b) at F3 and Fz, whereas the centroparietal components including N20 and P26 at C3 and P3 show no significant gating (left). No significant gating was seen in the counting task (right).

patients but not in controls (Figs 3, 5 and 8). All other SEP components showed no significant effect of task, group or task × group interaction. Representative topographical maps of the SEP in a control subject and a patient with writer’s cramp are shown in Fig. 6. There is a clear suppression of frontal N30 in the control subject, but not in the patient. Indeed, in this particular patient, N30 appears if anything to be enhanced by the movement task.

In a final analysis, we asked whether the amplitudes of SEPs at rest were different in the two groups. Two-way ANOVA on the resting data with component and group as main factors showed no significant main effect of group or group × component interaction. This suggests that the basal resting SEPs were similar in the patients and controls, although the amplitudes of central or parietal N34 in Patient 1 and frontal N30a in Patient 2 were larger than any of the normal subjects (Figs 4 and 5).

Because such large amplitude components in a few patients may comprise statistical outliers, we also analysed the data excluding those of Patients 2 (Fig. 5, outlined arrowheads) and Patient 9 (Fig. 5, circle), who showed remarkably large frontal N30 components. The result was the same as in the analysis using the whole data: paired t-test showed no significant difference between rest and movement in any component except for P22 amplitude at F3 (P = 0.015) in the patients.

Farfield P14 components (at P3, normal group: rest = 2.4 ± 1.4 µV, movement = 1.6 ± 2.1, count = 3.1 ± 1.5; patient group: rest = 2.2 ± 2.3 µV, movement = 1.6 ± 1.1, count = 2.7 ± 2.6) showed no significant effect of group or group × task interaction.

**Dystonic versus simple writer’s cramp**

No significant difference was found between the patients with dystonic (n = 6) versus simple (n = 4) writer’s cramp in the premovement gating of N30a/N30b components (a two-way ANOVA with components as main factors of group;
Abnormal gating of SEPs in dystonia

The onset time of the movement measured from rectified EMG amplitudes was 82.7 ± 5.6 ms in the control subjects and 84.0 ± 13.5 ms in the patients. A paired *t*-test showed no significant difference (*P* > 0.05) between the two groups. Furthermore, there was no significant correlation between the reaction time and gating of P22 (*r* = 0.15), N30a (*r* = 0.21) and N30b (*r* = 0.09).

**Reaction time**

**Background EMG activities**

The amount of background EMG activity, measured in the period from 10 to 50 ms after the stimulus, was the same in normal subjects and the patients, and was unaffected by task. (Control subjects: 14.6 ± 17.4 versus 15.6 ± 25.0 µV · ms in the rest and move conditions, respectively; patients: 16.9 ± 13.8 versus 16.9 ± 15.7 µV ms.) A two-way ANOVA with task and group as main factors showed no significant main or interaction effects. There was no significant correlation between background EMG activities and gating of P22 (*r* = 0.01), N30a (*r* = 0.02) and N30b (*r* = −0.25).

**Latencies of SEP components**

Only N30a at F3 was significantly different only at rest (*P* = 0.03, paired *t*-test) between the two groups (controls: 25.6 ± 2.1 ms; patients: 27.3 ± 1.0 ms). No significant change was seen between tasks in either group.

**Midmovement gating**

This study compared SEPs evoked in controls and patients at rest, and during active or passive joint movement. In dystonic versus simple and task; rest versus move), The amplitudes of these components at F3 were: N30a, 5.9 ± 7.0 µV at rest and 5.0 ± 6.9 µV in the movement condition; N30b, 2.5 ± 4.7 µV at rest and 1.8 ± 3.9 µV in the movement condition for dystonic writer’s cramp. In simple writer’s cramp the values were: N30a, 3.8 ± 2.9 µV at rest and 5.3 ± 2.2 µV in the movement condition; N30b, 2.4 ± 3.4 µV at rest and 2.9 ± 4.1 µV in the movement condition.

**Fig. 3** Grand averaged waveforms of SEPs following the right median nerve stimulation in the patient group (n = 10 in the ‘Rest/Premovement’ task and n = 8 in the ‘Rest/Count’ task). The data are shown as in Fig. 2. The mean reaction time measured from S2 to the rectified EMG onset was 83.2 ms. The premovement gating effect was seen only in the frontal P22 component at F3 (left). No other components showed gating, nor was there any gating in the counting task (right).
Fig. 4 SEPs from all normal subjects shown in superimposition (left = resting; right = premovement gating of SEPs, n = 11) at nine recording sites. The asterisks indicate the significant gating of each SEP component (*P < 0.05, **P < 0.01) analysed by paired t-test. The significant premovement gating effect on the frontal N30 components is seen at F3 and Fz, but less significantly at F4 and on the central N34 component at Cz.
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Fig. 5 SEPs from all patients shown in superimposition (left = resting; right = premovement gating of SEPs, n = 10) at nine recording electrodes. The asterisks are the same as in Fig. 4. The gating is significant only for the frontal P22 component at F3. Note that a few patients showed N30–P26–N34 amplitudes larger than in any normal subjects (cf. Fig. 4). Patients 2 (outlined arrowhead) and 9 (circle) showed large amplitude of frontal N30 components at F3 and Fz.
Table 2 Three-way ANOVA in the premovement gating: [group × all components × task (rest versus move versus count)]

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<th>Component</th>
<th>Group × component × task</th>
<th>F-value*</th>
<th>P-value*</th>
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<td>N30b</td>
<td>F(12,168) = 1.92</td>
<td>0.03</td>
<td></td>
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<tr>
<td>N30a</td>
<td>F(6,84) = 2.98</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Group × task</td>
<td>F(12,168) = 30.64</td>
<td>&lt;0.00001</td>
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<tr>
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<td>F(2,28) = 2.50</td>
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<tr>
<td>Group</td>
<td>F(1,14) &gt; 0.01</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td>F(6,84) = 51.32</td>
<td>&lt;0.00001</td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>F(2,28) = 5.71</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

*Results from repeated measures design of ANOVA.

Table 3 Two-way interactions in the premovement gating: [group × task (rest versus move)]

<table>
<thead>
<tr>
<th>Component Group × task</th>
<th>F-value*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P22 Normal–patient × R–M</td>
<td>F(1,19) = 12.38</td>
<td>0.002</td>
</tr>
<tr>
<td>N30a Normal–patient × R–M</td>
<td>F(1,19) = 15.87</td>
<td>0.0008</td>
</tr>
<tr>
<td>N30b Normal–patient × R–M</td>
<td>F(1,19) = 6.60</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Only significant results are shown. R = rest; M = premovement. *Results from ANOVA.

Table 4 Amplitudes of representative SEP peaks in the premovement gating and statistical analysis between different tasks

<table>
<thead>
<tr>
<th>Group Component</th>
<th>Rest amplitude (µV)</th>
<th>Move amplitude (µV)</th>
<th>Rest–move P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal P22</td>
<td>3.3 ± 1.6</td>
<td>4.3 ± 2.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>N30a</td>
<td>5.1 ± 3.3</td>
<td>2.7 ± 3.0</td>
<td>0.00006</td>
</tr>
<tr>
<td>N30b</td>
<td>3.6 ± 4.4</td>
<td>0.7 ± 3.2</td>
<td>0.002</td>
</tr>
<tr>
<td>N20</td>
<td>5.4 ± 2.1</td>
<td>5.5 ± 3.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>P26</td>
<td>6.8 ± 3.9</td>
<td>6.5 ± 3.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>N34 (Cz)</td>
<td>4.8 ± 3.7</td>
<td>3.6 ± 3.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Patient P22</td>
<td>4.7 ± 1.8</td>
<td>2.9 ± 2.9</td>
<td>0.002</td>
</tr>
<tr>
<td>N30a</td>
<td>5.1 ± 5.6</td>
<td>5.1 ± 5.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>N30b</td>
<td>2.4 ± 4.0</td>
<td>2.2 ± 3.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>N20</td>
<td>5.8 ± 2.9</td>
<td>5.5 ± 2.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>P26</td>
<td>5.1 ± 3.8</td>
<td>4.6 ± 4.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>N34 (Cz)</td>
<td>3.9 ± 4.0</td>
<td>3.9 ± 3.5</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation (µV). *Results from paired t-tests.

In contrast to the premovement studies, we found it impossible to distinguish two subcomponents of the frontal N30 potential (N30a and N30b) (Fig. 7). This may have been because of the increased stimulus rate (Garcia Larrea et al., 1992; Fujii et al., 1994) and/or the different bandpass filter settings that we used during recording. The same factors may also account for the smaller amplitude of the N30 potential compared with those in the premovement task (Garcia Larrea et al., 1992; Fujii et al., 1994). The following SEP components of P14 (P3), N20 (P3), P26 (P3) and N30 (F3) were measured in each subject.

The initial analysis involved all three tasks, all four SEP components and both subject groups in three-way ANOVA (see Table 5). This revealed not only a main effect of SEP component, but also a main effect of task, and task × SEP component interaction. There were no significant terms involving group, indicating that the patients and controls behaved similarly in these tasks.

Table 6 gives the amplitudes of each SEP component in the three tasks. Clear suppression of P14, N20, P26 and N30 (Fig. 8) is apparent for both controls and patients.

The compound nerve action potentials monitored from the elbow (normal group: rest = 9.8 ± 2.3 µV; active movement = 9.6 ± 2.2; passive movement = 9.4 ± 2.1; patient group: rest = 9.5 ± 2.5 µV; active movement = 9.3 ± 2.6; passive movement = 9.3 ± 2.5) were equal in both groups of subjects and were not affected by task (two-way ANOVA on amplitude of the response with task and group as main factors: no significant main or interaction terms).

Discussion

The present results showed that patients with writer’s cramp lack normal premovement gating of the frontal N30 component of the median nerve SEP, and have excessive gating of the P22 component. In contrast, midmovement gating of N20, P26 and N30 was normal. Because premovement SEPs were recorded in a reaction time paradigm, it is possible that they might have been contaminated with a slow CNV potential generated in anticipation of the appearance of the reaction signal. The fact that the CNV is smaller than normal in patients with writer’s cramp (Hamano et al., 1999) might have contributed to the difference in premovement gating. However, control studies in which we filtered out the slow component of the CNV suggested that this was not an important factor.

SEPs in dystonia

The present study was concerned mainly with components of the SEP that occurred around 30 ms after the stimulus was given. These were chosen for three reasons. First, because they occurred before the onset of movement and therefore could not be contaminated by afferents evoked by the movement itself; secondly, because they showed the largest gating effect of all the premovement components (Shimazu et al., 1999); and thirdly, because there is a large literature on the behaviour of frontal N30 in patients with dystonia (Nardone et al., 1992; Reilly et al., 1992; Mazzini et al., 1994; Grissom et al., 1995; Kanovsky et al., 1998) and other movement disorders (Rossini et al., 1989; Topper et al., 1993).

The origin of the frontal N30 is still a source of some debate. In intraoperative studies, Allison and colleagues demonstrated that components at that latency could be recorded directly from the surface of the posterior bank of the central sulcus (Allison et al., 1991). They suggested that the potentials arose by sequential processing of sensory input after arrival of N20 at the primary somatosensory cortex. In
Abnormal gating of SEPs in dystonia

Fig. 6 Scalp topography of the resting and the premovement SEPs obtained in a normal subject (43-year-old man) (A) and a patient (Patient 11) (B). Each voltage scale is coded in blue for negative and red for positive. Neither the normal subject nor the patient shows any change in amplitude of the central or parietal N20. N30 over the bilateral mid-frontal leads is attenuated before the movement in the normal subject, but not in the patient.

contrast, Mauguiere and colleagues showed that patients with focal frontal lobe lesions had a selective loss of P22–N30 potential (Mauguiere et al., 1983). They thought that sensory input had a separate input to the motor and premotor areas which was processed in parallel with the quicker route to the sensory cortex, as suggested by studies in the monkey (Lemon, 1979; Asanuma et al., 1980). The fact that we found movement to be more effective in gating frontal rather than parietal components at 30 ms is compatible with their idea.

There have been many studies of N30 in patients with dystonia, but the results have been conflicting. Reilly and colleagues studied SEPs in patients with writer’s cramp, using a stimulation rate of 1 Hz, and reported increased amplitudes of N30 (Reilly et al., 1992). Grissom and colleagues, on the other hand, used a very slow rate of stimulation (0.2 Hz) and showed a significant reduction of the N30 amplitude in patients with hand dystonia (Grissom et al., 1995). In patients with cervical dystonia, Mazzini and colleagues reported that the amplitude of N30 was reduced (Mazzini et al., 1994), while Nardone and colleagues found it to be normal (Nardone et al., 1992). Kanovsky and colleagues examined the effect of the head position in patients with cervical dystonia on median SEPs and found that the peak-to-peak P22/N30 amplitude was significantly reduced after botulinum toxin injection (Kanovsky et al., 1998). Our recordings in patients at rest showed no significant amplitude differences from those in the normal subjects, although a few patients displayed N30 amplitudes higher than any of the normal subjects. Instead the patients showed longer latencies of N30a at rest than those in the controls, but its significance is unknown.

Gating of SEPs

Two mechanisms contribute to the gating of SEPs. Central gating refers to changes in sensory transmission which are produced by commands that arise from within the central nervous system itself. For example, the efferent motor command can itself alter transmission of sensory input at cortical and subcortical levels (efferent gating). In addition, since SEPs can be gated several hundred milliseconds before the onset of movement (Bocker et al., 1993), it seems likely that the preparation to make a movement (‘central set’) can lead to similar changes in sensory transmission. Peripheral gating occurs when there is competition between afferents activated by the electrical stimulus and afferents activated by movement of the body. Gating that occurs before the onset of movement must be the result of central gating (Cohen and Starr, 1985, 1987; Cheron and Borenstein, 1987, 1991, 1992; Tapia et al., 1987; Chapman et al., 1988; Jones et al., 1989). In contrast, gating that occurs during passive movement (Rushton et al., 1981; Jones et al., 1989) must be
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Fig. 7 SEPs during active movement in a healthy 39-year-old man (A) and in a 45-year-old patient (Patient 20) (B). Not only the control subject, but also the patient shows decreased amplitude of the frontal N30 peak at F3 during midmovement. The amplitude of parietal N20/P26 is also decreased in both subjects. The compound nerve action potentials from the elbow (Elbow) showed no significant changes in either subject.

Table 5 Three-way ANOVA in the midmovement gating: [group × all components × task (rest versus active versus passive movement)]

<table>
<thead>
<tr>
<th></th>
<th>F-value*</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group × component × task</td>
<td>F(6,156) = 0.16</td>
<td>0.99</td>
</tr>
<tr>
<td>Group × component</td>
<td>F(3,78) = 0.10</td>
<td>0.96</td>
</tr>
<tr>
<td>Component × task</td>
<td>F(6,156) = 43.50</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Group × task</td>
<td>F(2,52) = 0.41</td>
<td>0.67</td>
</tr>
<tr>
<td>Group</td>
<td>F(1,26) = 1.36</td>
<td>0.25</td>
</tr>
<tr>
<td>Component</td>
<td>F(3,78) = 23.76</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Task</td>
<td>F(2,52) = 23.78</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

*Results from repeated measures design of ANOVA.

of peripheral origin. Gating during active movement may be due to a combination of both central and peripheral factors.

In normal subjects, conscious perception of evoked movement or cutaneous input is attenuated before and during voluntary movement (Collins et al., 1998; Milne et al., 1988). It is of interest that similar gating of muscle or cutaneous afferent occurs in the premovement period in a different paradigm, although, in our study, the subjective intensity of perceived stimuli was not quantified as in these studies.

Premovement gating of N30 was clear in the healthy subjects but was absent in the patients with writer’s cramp. Conversely, P22 was not gated in controls but was reduced in the premovement period in dystonia. Although there was some background EMG activity during the reaction time period, which could have affected SEP amplitudes through peripheral mechanisms, the amount was similar in both groups of subjects. There was no correlation between EMGs and N30 gating. Nor was there any difference in reaction times between the groups. We therefore conclude that the abnormal P22 and N30 gating in the patients is due to a disordered central mechanism in writer’s cramp.

A clue to the nature of this central abnormality comes from a careful examination of the design of the present experiments. Subjects began to prepare to move after the warning stimulus, but had to postpone their actual movement until after they had perceived the stimulus to the median
nerve. Thus, the premovement gating we observed must have been due mainly to changes in central sensory transmission produced by the intention of the subjects to move. Gating by any descending efferent motor commands must have been minimal since they could not have been issued until after arrival of the sensory stimulus at the cortex, by which time the SEP would have been generated. Indeed, the fact that both active and passive midmovement gating were normal suggests that peripheral and efferent gating mechanisms were relatively intact.

**Relevance of results to dystonia**

Although we do not yet know the precise mechanism of the premovement gating observed in the present experiments, several results from recent experiments in animals are likely to be relevant. In a warned reaction time experiment, neuronal activity in the premotor area and SMA as well as the basal ganglia and to a lesser extent in the primary motor area changes after the cue signal and continues until the imperative signal is given (Wise and Mauritz, 1985; Georgopoulos et al., 1989; Alexander and Crutcher, 1990a, b). This ‘set-related’
activity may be associated with the expected direction of the forthcoming movement, the order of the movements to be made, or the reciprocal activation of the muscles through the fusimotor system (Prochazka et al., 1985; Hulliger, 1987). In scalp recordings from man it may also contribute to the slow CNV potential that can be seen in an S1–S2 paradigm.

It is possible that the same neuromes are involved in generating the N30 component of the SEP. Thus, during the preparatory period, set-related activity may alter directly or indirectly the response of cells to afferent input, and gate the SEP response. Previous studies have shown that the CNV is smaller than normal (particularly in its late component) in patients with focal dystonia (Kaji et al., 1995a; Ikeda et al., 1996; Hamano et al., 1999). Thus, preparatory activity may be compromised, and in consequence gating of the N30 component may be reduced. In effect, we propose that dystonia is accompanied by a fault in the usual processes of movement preparation in the motor areas of cortex, for which we coined the term ‘motor subroutine’ (Kaji et al., 1995a, c). This activity may involve not only the specification of motor commands for a forthcoming action but also may alter the sensitivity of cells to afferent input.

In the circumstances of the present experiments, gating was abnormal only in the short period just before the onset of movement. During this period motor commands are presumably matched to the particular position of the body at that time (Evarts, 1981). Perhaps the abnormality of sensory gating in patients contributes to the incorrect choice of motor commands that characterizes dystonic movements. If so, then it might be possible, by changing sensory input, as with the sensory trick, to compensate to some extent for this disturbance and improve selection of the commands to move. Our patients showed normal gating during movement. However, their symptoms did not affect the task examined. Perhaps midmovement gating would also be affected in more severely affected patients who are unable to perform the task normally.

It has been proposed that sensory gating occurs in order to filter out the expected sensory consequences of movement so that resources can be focused on novel sensory inputs (Lidsky et al., 1985). Our results suggest that patients with dystonia have a problem in interpreting sensory input that occurs before, and perhaps in more severely affected patients even during movement. Indeed problems of dystonic patients in tests of stereognosis described by Byl and colleagues (Byl et al., 1996a), and vibratory induced movement illusions described by Grunewald and colleagues (Grunewald et al., 1997) fit well with this interpretation. Disorganized hand representation in the primary somatosensory area, as reported in patients with hand dystonia (Bara-Jimenez et al., 1998), may also contribute to this sensory–motor disintegration. Lenz and colleagues recently showed that sensory input to the thalamic nucleus Vim in patients with dystonia is transmitted through altered sensory maps, which could result in the overflow phenomenon (Lenz et al., 1999). In fact, abnormal central inhibition between dual SEP input, which indicates an overflow phenomenon in the sensory domain, was recently reported in dystonia (Tinazzi et al., 2000).

Interestingly, it has been suggested that basal ganglia play an important role in gating sensory inputs for guiding movements (Lidsky et al., 1985; Menon et al., 1998). Although the site of the lesion in primary dystonia is unknown, clinical studies in secondary dystonia suggest the basal ganglia and their connections to the thalamus and the cortex as a likely candidate (Marsden et al., 1985). One of the main hypotheses for the function of the basal ganglia is to control or select automatic movements after learning (Brotchie et al., 1991a, b). In fact, a recent human study showed activation of the pallidum after learning a motor task, and it was argued that the basal ganglia may act as a flexible system for learning the association of sensory cues and movements (Passingham et al., 1998). If this flexibility in associating sensory input and motor output is lost by, for instance, repetitious execution of a learned motor act such as writing, a fixed input–output mismatch may be the consequence. In support of this view, Byl and colleagues successfully produced an animal model of this condition by assigning an excessive and repetitious load of precision hand grip to a monkey, and found an extensive reorganization of the cortical hand sensory area (Byl et al., 1996b). Interestingly, a trauma to the affected body part, which may also disturb the input–output link, has been recognized as a risk factor to develop dystonia (Jankovic, 1994).

The symptoms of focal dystonia often appear only in certain tasks. In the present study, the patients performed the finger extension task normally. The changes in premovement gating in these patients indicate that the central abnormalities exist even for an unaffected movement. A similar dissociation of abnormal CNV and normal performance was reported in a previous study (Hamano et al., 1999). The latter also compared the CNV abnormality between the patients with task-specific (simple) writer’s cramp and those without task specificity (dystonic writer’s cramp), and showed no difference. The present study also failed to show any difference in the SEP gating abnormalities between them. These findings suggest that patients with task-specific symptoms may have a central compensatory mechanism that corrects the movement, as if taking advantage of a manoeuvre equivalent to the sensory trick. Alternatively, there may be a threshold of the central abnormality for producing clinical symptoms, which varies among patients.

The present experiments lead us to conclude that dystonia is not purely a motor phenomenon. It is also a disorder of sensorimotor integration. Indeed, this interpretation may apply to many of the other physiological abnormalities that have been described at all levels of the CNS in patients with dystonia. Abnormal cortical set may be reflected in subcortical structures, causing, for example, changes in spinal circuitry (Nakashima et al., 1989; Panizza et al., 1990) and the abnormal responses in tonic vibration reflex (Kaji et al., 1995b).

In summary, patients with writer’s cramp lack the normal
premovement gating of sensory input. This possibly involves a preconceived motor program (motor subroutine) that links sensory input and movement. Sensory inputs appear to play an important role at each level of the motor pathway involved in executing the program. Further neurophysiological investigation of focal dystonia is expected not only to clarify its pathophysiology, but also to gain more insights into the normal mechanisms involved in executing a specific task.

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