Neck proprioception and spatial orientation in cervical dystonia

Marco Bove,1 Giampaolo Brichetto,2 Giovanni Abbruzzese,2 Roberta Marchese2 and Marco Schieppati3

1Department of Experimental Medicine, Section of Human Physiology, 2Department of Neurological Sciences, Movement Disorder Unit, University of Genoa and 3Department of Experimental Medicine, Section of Human Physiology, University of Pavia, and Human Movement Laboratory (CSAM), Fondazione Salvatore Maugeri (IRCCS), Scientific Institute of Pavia, Italy

Summary
Neck muscle vibration is known to influence body orientation and posture during locomotion and stance in normal subjects. To verify the hypothesis that neck proprioceptive input can be misinterpreted in patients with cervical dystonia (CD), lateral continuous vibration was applied to the sternocleidomastoid muscle during both stepping-in-place and quiet stance, with eyes closed. The orienting responses of CD patients were compared with those of normal subjects. Vibration effects on body orientation during stepping and stance were apparently different from normal, since no effects were seen when all patients’ data collapsed were analysed. However, while some patients did not respond to vibratory stimuli regardless of the vibrated side, others had a ‘good’ side, the stimulation of which produced effects on body orientation similar to those observed in normal subjects. Homogeneous groups within the patient population were identified, based on the vibration-induced responses under stepping conditions. The different orienting or postural responses observed in CD patients were correlated with disease-related features such as spontaneous head position, maximum range of voluntary head yaw, presence or absence of a botulinum toxin treatment and disease duration. Our data suggest that, in CD patients, the reference system used in the control of body orientation in space is either refractory to the lateralized proprioceptive neck input or modified such that the input from both sides produces an orientation shift in the same sense. This would depend on the pathogenesis of the disease or an adaptive process connected to the head abnormal posture. It seems that this refractoriness spreads to both sides of the neck with the advancement of the disease, thereby possibly entraining a progressive shift from a reference system based on the head to a more reliable egocentric reference.

Keywords: cervical dystonia; neck muscle vibration; neck proprioception; quiet stance; stepping-in-place; spatial orientation

Abbreviations: BTX = botulinum toxin; C = control condition; CD = cervical dystonia; CFP = centre of foot pressure; CCW = counter-clockwise; CW = clockwise; SCM = sternocleidomastoid; Vl = vibration to the left side of the neck; Vr = vibration to the right side of the neck.


Introduction
Proprioceptive input from the neck muscles plays an important role in the definition of the reference system for the control of posture and locomotion. Cohen (1961) pointed to the weight of neck proprioceptive inputs in the control of body orientation and motor coordination in monkeys. In humans, several studies led to the notion that neck afferent input plays a significant role in the control of posture (Brandt, 1996) and that disturbances to the neck musculature can provoke dizziness or unsteadiness, the so-called ‘cervico-genic dizziness’ (Brandt and Bronstein, 2001). Hlavacka and Njikiktjien (1985) and Fransson et al. (2000) showed an influence of active and passive neck torsion on the direction of galvani- cally induced postural responses, an effect expected on the basis of the convergence of neck and labyrinth input onto...
brainstem nuclei (Pompeiano et al., 1991) and vestibular neur-
ons (Anastasopoulos and Mergner, 1982). Recently, a pro-
longed contraction of dorsal neck muscles has been shown to alter balance control through a mechanism connected to fatigue-induced afferent inflow (Schieppati et al., 2003).

Proprioception is often studied by means of muscle vibration, since this is an adequate stimulus for selectively activating the spindle receptor, thereby inducing a vibration frequency-entrained excitation of the primary endings and a train of action potentials in the large diameter afferent fibres (Burke et al., 1976a; Roll and Vedel, 1982; Matthews, 1988).

Lund (1980) showed that neck muscle vibration had obvious effects on standing posture. Vibration has also been applied to various body muscles under various behavioural conditions, including postural and locomotor tasks (Courtine et al., 2001). Lateral neck muscle vibration, in the absence of vision, produces undershoot of target and deviation of the trajectory during gait (Bove et al., 2001) and body rotation during stepping (Bove et al., 2002); under both conditions, the deviation is opposite to the vibration side. Ivanenko et al. (1999, 2000) showed that when the head is horizontally turned or the eyes are laterally rotated, vibration of dorsal neck muscles during stepping-in-place causes stepping in the direction of the naso-occipital axis or of the gaze, respectively. Ledin et al. (2003) found that head tilt on the sagittal plane, but not head rotation, produces changes in the postural sway induced by leg muscle vibration in standing subjects, thus confirming previous findings (Kogler et al., 2000) on the absence of major effects of head torsion on postural control.

The above effects can hardly be interpreted in terms of simple reflex effects. Goodwin et al. (1972) originally described proprioceptive illusions induced by muscle vibration. It was shown later that neck muscle vibration elicits apparent motion of a stationary visual target and deviation of the perceived 'straight ahead', possibly by producing a change in the egocentric body-centred coordinate system (Biguer et al., 1988; Taylor and McCloskey, 1991; Karnath et al., 1994). In standing subjects, neck muscle vibration induces body tilt and increased sway, suggesting that posture is organized with respect to a 'body schema', to the construction of which neck input contributes together with eye and skeletal muscle (Eklund, 1972; Roll et al., 1989; Gurfinkel et al., 1995; Ivanenko et al., 1999; Kavounoudias et al., 1999). In 'neglect' patients, neck muscle vibration can compensate the horizontal displacement of the sagittal midplane (Karnath et al., 1993; Karnath, 1994). Bottini et al. (2001) have shown recently that signals from the neck muscles and from the labyrinth converge onto several areas of the cortex, including the temporoparietal junction, the insular and retrolensular cortex and the secondary somatosensory area, and proposed the notion that these areas contribute to the egocentric representation of space.

Idiopathic cervical dystonia (CD) is the most common adult-onset focal dystonia and is defined as head rotation caused by an abnormal involuntary neck muscle contraction (Nutt et al., 1988; Jankovic et al., 1991). Recently, the existence of a pathogenetic role for sensory feedback in dystonia has been discussed (Hallet, 1995; Abbruzzese and Berardelli, 2003; Tinazzi et al., 2003). Sensory input may be abnormal and trigger focal dystonia, or its defective 'gating' may cause an input-output mismatch in specific motor programmes. Several observations strongly support the idea that sensorimotor integration is impaired in focal dystonia (Abbruzzese et al., 2001; Munchau et al., 2001; Siggelkow et al., 2002). Moreover, dorsal neck input in the context of whole-body postural control and spatial orientation seems to be relatively ignored in CD patients (Lekhel et al., 1997). These notions are consistent with results obtained in these patients by means of psycho-
physical studies of spatial orientation (Anastasopoulos et al., 1997a,b).

However, the matter is still controversial. A population of dystonic patients has been shown to exhibit altered postural control, and to improve their stance control after botulinum toxin (BTX) injection that normalized neck muscle activity (Wober et al., 1999). Other studies described a great variab-
ility in the capacity of CD patients to estimate their head and trunk direction; nonetheless, these patients appeared to estimate head and trunk displacements correctly in ego-centric and space-centric spatial orientation tasks (Anastasopoulos et al., 2003). The aim of the present study was to shed further light on the effect of neck muscle proprioception in CD patients, by using an experimental protocol recently developed, where neck muscle vibration is used to modify the reference system for spatial orientation during a dynamic, locomotor task (Bove et al., 2001). In particular, we report here the effects of lateral neck muscle vibration on body orientation during an extended stepping-in-place task without visual information. Such stim-
ulation induces in normal subjects a clear-cut body rotation to the side opposite to the vibrated side (Bove et al., 2002). We argued that lateral neck vibration during stepping would be a sensible enough protocol for answering the question of whether the proprioceptive neck input is ignored in CD patients in the context of spatial orientation, in which case no effect of vibration should be observed, or whether the neck input is centrally integrated in an abnormal way, in which case anomalous responses would be obtained. Stepping-in-place was used rather than linear locomotion, since stepping exhib-
ts several key characteristics of locomotion (Lyon and Day, 1997), in addition to allowing prolonged periods of locomotor-like activity to be recorded by means of a movement analysis system. The stepping-in-place paradigm has also been used extensively in the evaluation of patients with vestibular disorders (Norre et al., 1989; Bonanni and Newton, 1998), since the early observations by Fukuda (1959) of body rotation during stepping in normal subjects and vestibular patients.

In this work, the neck vibration was also administered to the same CD patients during quiet stance.

The orienting and postural responses of CD patients and normal subjects were therefore analysed and compared, in
order to understand whether, in CD patients: (i) a long-term neck vibration affected body orientation during stepping as in normal subjects; and (ii) vibration administered during quiet stance produced effects coherent to those observed during stepping. The responses were correlated with disease-related features such as spontaneous head position, maximum range of voluntary head yaw, presence or absence of a BTX treatment and disease duration.

Material and methods

Subjects

Twelve CD patients [four men and eight women, age range 33–82 years, mean 59 ± 15.1 (SD); mean disease duration 9.4 ± 5.5 years] and 12 normal subjects (seven men and five women, age range 31–76 years, mean 51 ± 15.5) volunteered for these experiments. All subjects gave their informed consent for the study, which was approved by the local ethics committee, and the study conformed to the Declaration of Helsinki. Normal subjects had no history of neurological diseases or signs or symptoms of cervical diseases or trauma. On clinical examination, subjects and patients showed no vestibular deficits or discrepancies between right and left lower limbs that can affect veering of locomotion (Boyadjian et al., 1999). In CD patients, both the amplitude of head deviation from the primary position (spontaneous head position) and the maximum range of the voluntary head rotation (yaw) were measured during quiet uprightness. These and other features are summarized in Table 1. Of the 12 patients studied, seven had received type A botulinum toxin (BTX-A) injections. The BTX-A treatment ranged between 10 and 40 BTX-A injections [mean 19 ± 11.3 (SD)] administered in several sessions. In most cases, the injected neck muscles were the sternocleidomastoid (SCM) controlateral to the head rotation, and one of the ipsilateral dorsal muscles. During the BTX-A treatment, the injections scheme was modified in some patients as a function of the head posture changes. Two patients had received BTX-A injections in both SCM muscles, and one had only the left dorsal muscles injected. All these patients were evaluated at least 3 months after the last injections. The remaining five patients, candidate for receiving for the first time BTX treatment, were evaluated before the injection.

Procedure

When they first came to the laboratory, subjects and patients practiced stepping-in-place, with eyes open and closed, for ~30 s before recording. For the experimental session, they were instructed to start stepping-in-place at their own preferred pace, on a verbal go signal until they were told to stop after 60 s. This was done under both control (C, no vibration) and vibration (V) conditions, in which case they were told not to react to the applied stimulation; in particular, there was no instruction to keep any pre-set facing direction or any definite head or body position. The CD patients were free to maintain their spontaneous head position during stepping. In different trials, vibration was delivered randomly to the right (Vr) and left side (Vl) of the neck. All subjects and patients easily succeeded in the stepping-in-place task in all trials and, within each trial, for the entire epoch of acquisition (1 min). The room was dim lit and the subjects kept their eyes closed during stepping. Under all conditions, the onset of acquisition of the kinematics signal started ~3 s after the verbal go signal for stepping onset. By this time, subjects and patients had already performed at least one or two complete stepping cycles. For V, the vibrator was set on concurrently with the onset of the acquisition. The vibrator and the acquisition were shut off 60 s later, at the end of the trial. Two trials were performed randomly for each C, Vr and Vl condition (six trials in total). The entire session lasted ~60 min, including rest periods. After the session, subjects were asked specifically about head tilt or rotation illusions: under no circumstances did normal subjects or CD patients report explicit sensations of head turning or tilting on the trunk in response to the vibration. This is not contradictory to the finding reported in the study of Taylor and McCloskey (1991), where dorsal neck vibration rarely produced illusions of head movement. We did not check,

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration (years)</th>
<th>Type of cervical dystonia</th>
<th>Associated signs</th>
<th>Treatment and SCM muscle injected</th>
<th>Head deviation (°) (+, R; −, L)</th>
<th>Max head voluntary rotation (°)</th>
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<tr>
<td>1</td>
<td>F</td>
<td>45</td>
<td>11</td>
<td>Rotatocollis (R)</td>
<td>Head tremor</td>
<td>BTX-A, R/L</td>
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<td>32.6</td>
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<td>2</td>
<td>M</td>
<td>82</td>
<td>13</td>
<td>Rotatocollis (R)</td>
<td>–</td>
<td>BTX-A, L</td>
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<td>41.3</td>
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<tr>
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<td>F</td>
<td>62</td>
<td>4</td>
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<td>BTX-A, R</td>
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<td>22.3</td>
</tr>
<tr>
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<td>F</td>
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<td>11</td>
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<td>−24.7</td>
<td>78.3</td>
<td>111.8</td>
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<td>55</td>
<td>3</td>
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<td>22.0</td>
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<td>M</td>
<td>47</td>
<td>13</td>
<td>Rotatocollis (L)</td>
<td>–</td>
<td>BTX-A, R; AC</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
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<td>6</td>
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<td>8</td>
<td>F</td>
<td>42</td>
<td>2</td>
<td>Rotato- and laterocollis (L)</td>
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<td>72.0</td>
<td>123.1</td>
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<tr>
<td>9</td>
<td>F</td>
<td>76</td>
<td>6</td>
<td>Rotatocollis (R)</td>
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<td>BTX-A, L</td>
<td>44.5</td>
<td>5.2</td>
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<tr>
<td>10</td>
<td>F</td>
<td>70</td>
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<tr>
<td>11</td>
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<td>21</td>
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<td>BTX-A</td>
<td>8.3</td>
<td>39.9</td>
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</table>

R = right; L = left; BTX-A = botulinum toxin type A; AC = anticholinergics; SCM = sternocleidomastoid.
however, whether vibration produced errors in the execution of movements pointing at a specific spot in the head.

In a separate session, three of the normal subjects performed additional stepping-in-place trials, in C and V conditions, with the head deliberately kept rotated $\sim 20^\circ$, first on the right and then on the left side. Five other naïve subjects (two men and three women, age range 24–40 years, mean 29.6 ± 6.2), who did not participate in the main experiment, were also recruited for this experiment. This was done to check, first, any effects of static head yaw on body rotation during stepping under control condition and, secondly, possible differences in the effects of neck muscle vibration on stepping orientation when the head was in the primary position versus rotated to an extent comparable with the spontaneous position of the head in many CD patients. These subjects repeated three trials for each condition.

All normal subjects and CD patients who participated in the stepping-in-place sessions also stood upright on a dynamometric platform, on the same day, after a rest period of at least 10 min (see below).

Stimulation
A DC motor with an eccentric on the shaft, embedded in a plastic tube (Dynatronic, France), produced 5 N peak-to-peak vibrations at 90 Hz. The vibrator was applied on each side of the neck (left and right sides were vibrated separately) by means of an elastic strap that passed around the neck. The vibrated spot was the belly of the SCM muscle, ~40% of its length below its insertion on the mastoid (~5–6 cm from the mastoid apex), with the cylinder axis about normal to the direction of muscle. The vibrator was put in place at the beginning of the experiment and kept in place throughout the session. In order to evaluate the propagation of the vibration to the temporal bone, which could possibly induce activation of the labyrinthine receptors, in three normal subjects we used two identical accelerometers (TSD109, BIOPAC Systems Inc., Santa Barbara, CA), one fixed to the vibrator located on the muscle, the other placed on the ipsilateral mastoid bone. The amplitude of the main peak in the power spectrum of the vibration signal recorded at the mastoid bone was, on average, $<1%$ (0.66 ± 0.03%) of the signal measured at the muscle. This finding indicates a negligible propagation of the mechanical wave to the labyrinth, and strongly lessens the likelihood of vestibulum-mediated vibration effects.

Kinematics
Body movements were recorded by an optoelectronic motion analysis system (ProReflex, Qualisys AB, Sweden). Four infrared cameras were located around the experimental field, identifying a space of $\sim 2.5 \times 2.5 \times 2.5$ m. The reflective markers were attached to the skin on the forehead, vertex of the head, left and right acromion and on the right lateral femur epicondyle. Two markers on the floor identified a fixed reference axis. The markers’ position was sampled at a frequency of 100 Hz. The following parameters were computed for each trial and under each condition (C, Vr and Vl). (i) Step cycle frequency. The recording of the vertical displacement of the knee versus time was subjected to a fast Fourier analysis and the value of the main peak was taken as the mean value of step frequency. (ii) Body displacement. The first and last 100 samples of this angle value (recorded at the beginning and the end of each trial) were averaged. The initial mean position was then subtracted from the final mean position. In normal subjects, the body rotation was ~0 in the control condition, and could become negative or positive when the neck was vibrated on the right or left side of the neck, respectively (Bove et al., 2002). Negative values indicate a counter-clockwise (CCW), and positive values a clockwise (CW) rotation. (iv) Head–shoulder angle (yaw). This was the mean angle between head antero-posterior axis and shoulder medio-lateral axis evaluated during stepping-in-place.

Stabilometric recording

The sampling frequency of the force exerted on three strain gauges of a dynamometric platform (Medicapteurs, Toulouse, France) was set at 10 Hz. The subjects were asked to stand still with their eyes closed, their bare feet on a patterned surface at an angle of $30^\circ$, with their heels separated by 10 cm, and their arms kept at their sides. Each trial lasted 51.2 s, regardless of the condition tested. The vibration was applied to the same spot and side as in the stepping-in-place sessions. The antero-posterior and medio-lateral displacement of the centre of foot pressure (CFP) was measured: (i) during the stance trials without vibration (C); (ii) during Vr; and (iii) during Vl. The trials were spaced by at least 3 min, during which subjects were allowed to move across the laboratory in order to allow recovery from possible long-lasting effects of vibration (Wierzbicka et al., 1998) and from the effects of repetition of stance trials (Tarantola et al., 1997).

Statistical analysis

The effects of vibration on stepping frequency, body displacement, body rotation, head–shoulder angle and displacement of CFP were assessed by means of an analysis of variance (ANOVA) for each subject in each experimental condition. Homogeneity of data variances was evaluated by means of the Bartlett’s test. Comparisons within groups or between groups (normal subjects or CD patients as independent variables) were performed by means of a one-way or two-way repeated measure ANOVA, respectively, where the dependent variables were the three different experimental conditions (C, Vr and Vl). When repeated measure ANOVA gave a significant ($P < 0.05$) result, the post hoc Newman–Keuls test was employed to assess differences among C and V conditions for both the stepping-in-place and quiet stance protocol.

Linear regression analysis was used to evaluate, in CD patients, the possible relationship between head yaw angle and CFP mean position in the sagittal and frontal plane during quiet stance, or between head yaw angle and body rotation angle during stepping-in-place.

Results

Stepping-in-place

Stepping frequency
In CD patients, a lower and marginally significant stepping frequency with respect to normal subjects was observed...
within all the experimental conditions (normal subjects, C, 0.93 ± 0.02 Hz; Vr, 0.9 ± 0.019 Hz; Vl, 0.9 ± 0.018 Hz; CD patients, C, 0.75 ± 0.07 Hz; Vr, 0.76 ± 0.08 Hz; Vl, 0.77 ± 0.08 Hz; means ± SE) [two-way repeated measure ANOVA, \( F(2,44) = 4.1; P = 0.05 \)]. Neck muscle vibration (V) administered during stepping did not modify the stepping frequency with respect to C, in either normal subjects or CD patients [two-way repeated measure ANOVA, \( F(2,22) = 0.275; P = 0.76 \)].

**Body displacement**

The effect of the vibration on the capacity of subjects and patients to step on the spot was evaluated by the distance between their final and initial body positions. The mean distance from the starting position is indicated in Fig. 1A (normal subjects) and B (CD patients) by the length of the dashed lines radiating from the origin of the polar plots.

In normal subjects, under C, Vr and Vl conditions, there was an average body displacement of 58.2 ± 37.6, 59.3 ± 29.4 and 52.5 ± 22.8 cm (SD), respectively. This body displacement was usually oriented forward under the control condition. The displacement was instead directed to the left or to the right when the vibration was applied to the right and left side of the neck, respectively (Fig. 1A). Regardless of the actual direction of the stepping, the final distance attained during vibration did not show significant changes with respect to the control condition (Vr versus C, \( P = 0.88 \); Vl versus C, \( P = 0.45 \)).

In CD patients, the average body displacement was 94.9 ± 51.9, 83 ± 42.8 and 74.2 ± 44.7 cm (SD), in C, Vr and Vl conditions, respectively (Fig. 1B). The difference in the body displacement between normal subjects and patients, all conditions pooled, was only marginally significant [two-way repeated measure ANOVA, \( F(1,22) = 4.27; P = 0.051 \)]. A marginally significant difference across conditions was present for the CD patients [two-way repeated measure ANOVA, \( F(2,44) = 3.16; P = 0.052 \)]. In fact, the body displacement in both V conditions was lower than that observed in the control condition, but only in the Vl condition was the difference significant (\( P = 0.02 \)).

**Body rotation**

Normal subjects and patients could rotate slightly on their vertical axis during stepping-in-place under control conditions. In the normal subjects, a slow yet continuous body rotation was the main and consistent effect of the lateral
neck vibration. In the patients, the rotation during stepping was less consistent (see below). The mean rotation values attained by the populations of normal subjects and of CD patients at the end of the stepping trial are represented by the angular coordinate of the dashed lines radiating from the origin of the polar plots in Fig. 1A (normal subjects) and B (CD patients).

Normal subjects exhibited no major rotation under control condition, as indicated by the mean value, very close to 0° (1.2° CCW, dashed black line), and by the small data variance, as indicated by the two 95% confidence limits (continuous black lines) (see Fig. 1A). Under vibration conditions, there was a systematic rotation, in the direction opposite to the vibrated side. In the figure, the scatter of the rotations induced by right and left vibrations are indicated by the sectors between the continuous dark grey and light grey lines, respectively, which correspond to the two confidence limits. On average, the rotation was ~53° CCW and 68° CW with respect to the initial body position, for vibration applied to the right and left neck side, respectively. These values were significantly different from the negligible rotations observed under the control condition [two-way repeated measure ANOVA, $F(2,44) = 29.06; P < 0.005$ for Vr, and $P < 0.0001$ for VI]. The distribution of the rotation data around the population mean value was similar across the two vibration conditions (Bartlett’s test: $P = 0.34$).

CD patients exhibited a much smaller consistency in body rotation than normal subjects under control conditions, in spite of their average orientation being similar to that of normal subjects (Fig. 1B). The average final position of the population was rotated by only a few degrees (7.8° CW) with respect to the initial position. However, the scatter of the rotation data was much larger across the patients’ population, as indicated by the broad sector comprised between the 95% confidence intervals, and the variance of the data obtained under control conditions proved to be different between normal subjects and CD patients (Bartlett’s test: $P < 0.001$).

CD patients as a population showed no significant difference in body rotation between vibration and control conditions (Vr versus C, $P = 0.09$; Vl versus C, $P = 0.56$). The amplitude of the confidence interval was similar under control and vibration conditions, but was about twice that observed for the normal subjects (under any conditions). The variance of the data recorded under the C and V conditions proved to be different between normal subjects and patients (Bartlett’s test, C, $P < 0.01$; Vr, $P < 0.01$; Vl, $P < 0.01$). This scatter, however, was more of a population result rather than the expression of inconsistencies within patients’ performances. To show this, the absolute differences between the rotations of the two trials performed by each patient under each condition were averaged and compared in the two populations: no significant difference between normal subjects and CD patients was observed in this value [two-way repeated measure ANOVA, $F(2,44) = 1.17; P = 0.32$], indicating a similar variability in each of the subjects of the two groups.

Therefore, the responses to vibration of the individual CD patients were reproducible, as were those in the normal subjects, in spite of their responses being sometimes very different in absolute terms from those of normal subjects. In fact, in the normal subjects, the confidence interval of the responses to each vibration condition covered only one quadrant of the polar diagram. Conversely, in the CD patients, the range between the confidence intervals of the rotations under each vibration condition partly overlapped around zero. This is the outcome of a non-systematic response pattern to vibration across the whole group of CD patients: CCW and CW responses alike could occur in fact for the same neck vibration side in different patients.

The mean position of the head on the vertical axis with respect to the body sagittal plane was evaluated in normal subjects and CD patients during the stepping-in-place under all conditions. Under control conditions, normal subjects had a mean head yaw angle of $-0.08 \pm 0.9°$ (SE) (Fig. 1C), while in the patients this mean angle reached $-3.8 \pm 3.9°$ (Fig. 1D). Interestingly enough, the mean head yaw angle during the stepping trials underwent no significant vibration-induced changes across any condition. This was true for both the normal subject group [one-way ANOVA, $F(2,22) = 0.006; P = 0.99$] (Fig. 1C) and the patient group [one-way ANOVA, $F(2,22) = 1.14; P = 0.34$] (Fig. 1D).

**Patient groups according to their responses**

To better describe the responses to neck vibration in CD patients, data were analysed in each single patient, in order to extract potential features common to other patients of the same population, and possibly identify homogeneous subgroups. The same data for the normal subjects population, and allows a comparison of the vibration effects on body rotation in the two groups. Dashed lines are the limits of the 95% confidence interval of the body rotations evaluated within all the CD patients (Fig. 2A) and normal subjects (Fig. 2B) under control conditions. The interval thus identified is considered, for each group, as the zone where the neck vibration effects on the body rotation are non-significant. The bars are the mean rotation values calculated from the two trials accomplished during vibration of the same side. Across normal subjects, the amplitude and sign of the vibration-induced rotations were very consistent: all subjects rotated CW on Vr and CCW on Vl. Across the patients, vibration induced two main patterns. (i) The responses to vibration applied to both the right and the left side lay inside the confidence interval. Five of the 12 patients (subjects 2, 3, 4, 6 and 11) had this kind of response. Henceforth, these patients are indicated as belonging to a group ‘insensitive’ to vibration stimuli (INS group). (ii) The body rotations in response to vibration were significantly different from those observed under control conditions (and congruent with the responses observed in the normal subjects) when one side of the neck was vibrated, but they were either non-significant...
or were incongruent when the other side of the neck was vibrated, since the body rotated in the ‘wrong’ direction compared with normal subjects’ rotation. Hence, there was in this group one ‘sensitive’ side and one ‘insensitive’ or ‘wrong’ side (note, however, that the wrong rotations never exceeded the correct response on contralateral stimulation). Seven patients showed this pattern, and were divided in turn into two subgroups related to the neck side, the vibration of which induced the ‘correct’ response (the RIGHT group consisted of subjects 8, 9 and 12; the LEFT group consisted of subjects 1, 5, 7 and 10).

Figure 3A, B and C summarizes the mean responses to lateral neck vibration of INS, RIGHT and LEFT groups, respectively. As expected, the INS group (Fig. 3A) showed no significant rotation under vibration or control conditions [one-way repeated measure ANOVA, $F(2,8) = 1.95; P = 0.2$], while the RIGHT (Fig. 3B) and LEFT (Fig. 3C) groups were selectively and significantly sensitive to vibration [one-way repeated measure ANOVA: RIGHT group, $F(2,4)= 10.44; P < 0.05$; LEFT group, $F(2,6) = 6.13; P < 0.05$]. The mean RIGHT group response to right vibration was a CCW rotation of $\sim 111^\circ$ (Vr versus C, $P < 0.05$), while left vibration induced no significant effects. Conversely, the LEFT group rotated CW $\sim 83^\circ$ for vibration to the left side (Vl versus C, $P < 0.05$), and no significant rotation was induced by right side vibration. Interestingly, the variability of the vibration-induced body rotations within each of these groups, in spite of the small number of patients, was of the same magnitude as that in the normal subjects population.

**Head–shoulder angle (yaw) versus body rotation angle**

The spontaneous head yaw mean angles ranged between 3 and 50° in the CD patients. We tested the hypothesis that the head position could affect the vibration-induced body rotation. Since it is known (Leis et al., 1992; Lekhel et al., 1997; Karnath et al., 2000) that neck muscle vibration can produce sizeable effects on head yaw in CD patients, we recorded head yaw relative to trunk during vibration. The plot in Fig. 4 shows, for each patient, the mean head yaw during Vr and Vl (ordinate) versus the spontaneous head yaw. Across the patients, there were no major vibration-induced changes, as indicated by the data points clustering close to the identity line. There were non-negligible effects in some patients, but the effects were apparently not side specific in this population. Moreover, there was apparently no difference in the vibration-induced effects on head yaw among the three patient groups, as defined above (INS, RIGHT and LEFT), since the data of the patients belonging to these groups formed no clear clusters in the scatterplot.

The possible effect of the head posture on the body orientation during stepping-in-place was then analysed across individual patients stepping under both control and vibration conditions. All individual trials from all the patients were segregated in Fig. 5, which shows the scatter graphs of body rotation angles against head yaws, for C (Fig. 5A), Vr (Fig. 5B) and Vl (Fig. 5C) conditions. No significant relationships between head–shoulder angle and body rotation angle were found either in C or V conditions (C, $P = 0.26$; Vr, $P = 0.12$; Vl, $P = 0.095$). Similar results were found in normal subjects (C, $P = 0.61$; Vr, $P = 0.59$; Vl, $P = 0.59$), as already shown in Bove et al. (2002).

**Head deliberately rotated in normal subjects**

Eight normal subjects stepped with eyes closed with the head rotated to either side to an extent similar to that found in the
patients (Fig. 6A). Under the control condition, no or non-systematic body rotations were observed, across subjects or trials (Fig. 6B). The mean head–shoulder yaw angles were (mean \( \pm \) S.E): head in primary position, 0.68 \( \pm \) 1.17°; left rotation, -28.74 \( \pm \) 3.11°; right rotation, 22.83 \( \pm \) 2.64°. These head positions were also broadly maintained during vibration. The vibrations, on either the right or the left side, induced significant and systematic CCW and CW body rotations, respectively (Fig. 6B) [two-way repeated measure ANOVA, \( F(2,42) = 91.28; P < 0.001 \)]. The analysis also confirmed that head position did not affect the vibration-induced body rotation [two-way repeated measure ANOVA, interaction effect, \( F(4,42) = 0.96; P = 0.44 \)]. The deliberate head rotation did not significantly affect the absolute value of the responses to vibration compared with those observed with the head in the primary position (post hoc, left rotation in both Vr and VI, \( P > 0.1 \); right rotation in both Vr and VI, \( P > 0.1 \)). To assess whether the variability of the body rotation angles during stepping was affected by the head posture (possibly producing a scatter in the data comparable with that seen in the CD patients), the data obtained in these trials with the head deliberately rotated were compared with those obtained in the population of normal subjects stepping with the head in the primary position, illustrated in Fig. 1A. The homogeneity of variances between these two sets of data was confirmed by the Bartlett’s test (\( P = 0.19 \)).

**Upright stance**

**Antero-posterior CFP position**

Under control conditions, CD patients were inclined forward, on average, somewhat more than normal subjects (Fig. 7). Their CFP lay significantly ahead with respect to that of normal subjects [two-way repeated measure ANOVA, \( F(1,22) = 12.96; P = 0.0015 \)]. Across the patients, there was no relationship between the spontaneous head yaw angle and the CFP position in the sagittal plane (\( F = 0.33; P = 0.58 \)). Vibration exerted no significant effect on the antero-posterior position of the CFP in either normal subjects.
Medio-lateral CFP position

Under control conditions, the medio-lateral CFP position was not different between normal subjects and CD patients (Fig. 7). As for the antero-posterior plane, there was no significant regression between spontaneous head yaw angle and CFP position in the frontal plane ($F = 0.085; P = 0.78$).

Lateral neck muscle vibration induced in the normal subjects a significant CFP displacement in the frontal plane with respect to C (Fig. 7), the amplitude of which was in turn compatible with published data (Bove et al., 2001). In particular, $V_r$ induced a shift to the left and $V_l$ to the right. In the CD patients, vibration had a much weaker effect on medio-lateral displacement of CFP. Two-way repeated measure ANOVA showed an effect of group (normal subjects versus CD) and an interaction between groups and conditions. In particular, significant differences in the medio-lateral CFP displacements induced by vibration were observed between normal subjects and CD patients [$F(2,44) = 11.71; P < 0.001$]. Post hoc test showed a significant side-related effect of vibration in normal subjects ($P < 0.001$), but no effect in CD ($P = 0.11$). Therefore, on average, the patients had a smaller sensitivity to vibratory stimuli than normal subjects under quiet stance as well as under stepping-in-place condition.

Effects of vibration during stance in the patients’ groups

The patients’ CFP was re-analysed based on the separation in the three groups defined on the basis of the findings collected with the stepping-in-place protocol, and the postural responses to neck vibration of the three groups compared separately. Figure 8A, B and C shows the mean postural responses to lateral neck vibration of the INS, RIGHT and LEFT groups, respectively. The INS group did not show significant differences in medio-lateral CFP displacement during either $V_l$ or $V_r$ conditions [one-way repeated measure ANOVA, $F(2,8) = 2.58; P = 0.137$]. However, during $V_r$ conditions, a significant backward displacement of the CFP along the sagittal plane with respect to C was observed [one-way repeated measure ANOVA, $F(2,8) = 4.79; P = 0.043$]. This displacement (a mean shift to the left on the frontal plane of $\sim 12$ mm) was significant only for $V_r$ ($P < 0.05$). In contrast, $V_l$ induced only a slight and non-significant medio-lateral displacement with respect to C ($P = 0.093$) in the ‘wrong’ direction (to the left), compared with the response observed in the normal subjects group under the same condition (Fig. 7).

In the LEFT group, no significant vibration effects on CFP displacement on the sagittal plane were observed [one-way repeated measure ANOVA, $F(2,6) = 0.69; P = 0.54$]. However, in this group, the CFP position in the frontal plane was significantly sensitive to $V_l$ [one-way repeated measure ANOVA, $F(2,6) = 4.62; P = 0.046$]: a displacement to the left was observed ($P < 0.05$).
right of ~15 mm was induced by Vl, while Vr did not exert any influence on CFP medio-lateral displacement ($P = 0.99$).

Discussion

Stepping-in-place

Lateralized neck muscle vibration, applied during stepping-in-place with the eyes closed, is known to induce clear-cut body rotation and a moderate displacement from the starting position in normal young subjects. The rotation is invariably toward the side opposite to the vibrated site, i.e. CW on left and CCW on right side vibration, respectively, and the displacement is in the forward direction (Bove et al., 2002). The normal subjects recruited in the present study, who represented a population age-matched to the CD patients, reproduced the same patterns of body displacement observed in the young subjects under control conditions and in response to vibration.

Forward displacement

The CD patients showed significant differences from normal subjects in their body progression during stepping-in-place, under control conditions. Forward body displacement was almost twice as large as that observed in normal subjects. The body therefore moved with a relatively higher velocity than in normal subjects, since the trial duration was constant. It is worth noting that the stepping frequency of CD patients was significantly lower than that of normal subjects, thus patients take ‘longer steps’ than normals. The significantly lower stepping frequency in CD patients would be in keeping with the occurrence in these patients of ‘parkinsonian symptoms’ such as bradykinesia (Couch, 1976). The increased step length should not be taken as a contradiction, since we do not deal here with true locomotion, and the ‘high’ velocities were in the order of 1 m/min. These incongruities may rather
indicate for CD patients a greater difficulty than normal subjects to step ‘in place’ without visual information.

Vibration of the SCM muscle did not modify forward displacement in normal stepping subjects, but in CD patients it reduced the distance reached. Ivanenko et al. (2000) showed that, during stepping-in-place, dorsal neck vibration produced in normal subjects an involuntary forward stepping, which has been explained as the consequence of an illusion of forward movement of the head or forward sway (Lund, 1980; Lekhel et al., 1997) to which the appropriate response is to step forward. In our case, the vibration was not acting on dorsal muscles; indeed, normal subjects did not increase their progression rate. It is curious nonetheless that CD patients reduced their progression with vibration, while a forward progression might perhaps have been expected as an effect of diffusion of the vibration to the dorsal muscles, not least because of the abnormal head position.

**Body rotation**

The CD patients exhibited a much smaller consistency in body rotation than normal subjects under control conditions, as proved by a significant difference between the data variances, in spite of their average orientation being similar to that of normal subjects. The effects of the neck muscle vibration on body rotation during stepping were also different from normal, since when the collapsed data from all patients were analysed, there was no effect of vibration on body rotation. In fact, no significant difference in the average body rotation during vibration, either on the left or on the right side, was detected with respect to their average rotation under control conditions. This could have been the outcome of a smaller sensitivity to vibration in CD patients or of a ‘wrong’, abnormal response to lateral neck vibration, or both. However, one of the reasons for the lack of a systematic vibration-induced body rotation in CD patients proved to be the ample variability in the body rotation across subjects, under both vibration and control conditions. This was in fact reflected in a confidence interval of the population data that was about twice as large as and significantly different from that observed for the normal subjects, under any condition.

**CD patients’ groups**

This analysis of the responses of each patient gave the possibility to extract potential common features and to identify homogeneous groups within the population of CD patients. In fact, it soon appeared that there were patients who did not rotate, regardless of the vibrated side, or patients who had a ‘good’ side, the stimulation of which produced effects on body rotation similar to those observed in normal subjects. It also appeared that no CD patient exhibited a fully normal response (CW on Vl and CCW on Vr); rather, patients were refractory to vibration on either or both sides of the neck. In those with one good side, the contralateral side could be refractory or exhibit the same response observed on the vibration of the good side, as if the CNS could produce one and the same type of rotatory response on receiving the proprioceptive input from either side of the neck. CD patients could then
be classified into three groups, according to their complete (INS) or partial (RIGHT or LEFT) sensitivity.

**Head abnormal posture is unrelated to abnormal body orientation response to vibration during stepping-in-place**

A concern was represented by the possibility that the spontaneous head abnormal posture of CD patients would ‘determine’ the body rotation induced by the lateralized neck vibration, either because of the ongoing asymmetrical ‘natural’ input possibly being able to modify the orientation of stepping or because during vibration it could counteract in some way the effect of the asymmetrical neck muscle proprioceptive input. A further concern was represented by the possibility that lateral neck muscle vibration would produce head-on-shoulder rotation in both normal subjects and patients, in turn possibly affecting the orientation of the body during stepping. Neck muscle vibration in fact has been reported to induce involuntary movements of the head in some patients (Lekhel et al., 1997; Karnath et al., 2000). A still further concern was that the changes in muscle length or contraction level or in passive or active stiffness of the vibrated muscles, due to the head posture, could modify the mechanical effect of the vibratory stimulus (Burke et al., 1976b).

However, during the stepping trials, no significant changes in the head primary position were observed on lateralized neck vibration in normal subjects. In the control experiments on normal subjects, with the head deliberately turned, with or without vibration, no significant relationship between head yaw angle and body rotation angle was observed across subjects and conditions, as already reported in Bove et al. (2002). The spontaneous head position (yaw) did show some vibration-induced changes in a few CD patients; however, no significant relationships between head yaw angle and body rotation angle during stepping-in-place across all the patients and conditions (control and vibration) were observed. Further, it might be noted that these relationships were characterized by a similar slope, to underscore again a general lack of dependence of spatial orientation effects on head postural response to vibration of CD patients.

In spite of the variability across subjects, the absence of significant body rotation when the head was deliberately turned, in the normal subjects under both no vibration and vibration conditions, points to the irrelevance of the natural asymmetric neck input on the body rotation during the stepping trial. This result would be taken as evidence against the possible influence of the muscle stiffness on the vibration-induced afferent volley, because if stiffness or contraction had conditioned the efficacy of the vibration, the spindle input from the vibrated muscle would be expected to change depending on the muscle being active and shortened or being passive and lengthened during the head rotations.

In the treated patients studied here, the single dose of the BTX was within the range commonly used in CD treatment (between 15 and 100 IU). Further, the behaviour of the groups did not differ with respect to the spontaneous head position, BTX treatment and maximum range of voluntary head yaw (Fig. 9). Interestingly, the spontaneous angular head deviation with respect to the primary position (Stell et al., 1988; Tsui et al., 1996) was not correlated with the degree of maximal voluntary rotation of the head in any of the three groups. All these features suggest that the absent or limited insensitivity to vibration was not directly related to the disease effects on the neck torsion (see below). In addition, CD patients who had never received the BTX treatment showed the same responses as the other patients. Moreover, treated and untreated patients were distributed in the different CD groups and they shared the same mean features for both spontaneous head position and maximum head rotation angle of the other patients. This would exclude the possibility that the observed ‘insensitivity’ was caused by the BTX injections, through its effects on spindle afferent activity as seen in rat (Filippi et al., 1993; Rosales, 1996) and humans (Priori et al., 1995; Naumann and Reiners, 1997; Gilio et al., 2000). We do not know whether larger doses or a longer period of BTX-A treatment could affect the spindle’s transduction properties, or whether long-term effects of the BTX could induce any effect on spindle sensitivity. However, we observed that the two patients who received several BTX-A injections on both SCM muscles showed only a partial insensitivity to vibratory stimuli, while other patients treated only on one neck side fall within the INS group.

**Quiet stance**

Under this condition, lateral neck vibration produces a mediolateral body displacement, opposite to the side of the vibration

Fig. 9 Maximum voluntary head rotation angle in the horizontal plane plotted against mean spontaneous head position in CD patients. Patients were identified with different symbols for each group. Black filled symbols correspond to the five BTX-A-untreated patients.
(Eklund, 1972; Bove et al., 2001, 2002) and it did so in our normal subjects tested during stance. In CD patients, during quiet upright stance, the effects of neck muscle vibration were different from normal, since when all the patients’ data collapsed were analysed, there was no effect of vibration on posture. The absence or reduction of postural responses was also seen by Lekhel et al. (1997) when the dorsal neck muscles were vibrated.

Interestingly enough, during quiet upright stance, patients belonging to the RIGHT and LEFT group revealed behaviours reminiscent of that observed under the stepping-in-place condition. In fact, these patients correctly responded only to vibration of the same side of the neck that produced rotation during stepping-in-place. It should be noted that in both stepping-in-place and upright stance conditions, the ‘correct’ responses of CD patients implied body rotations or mediolateral displacements of similar amplitude to those observed in normal subjects. The INS group showed no significant mediolateral displacements induced by vibration during stance, and the same insensitivity to vibration was observed during stepping-in-place. However, a small backward displacement occurred, which was significantly different with respect to the control condition when either side of the neck was vibrated. This effect might be explained as a postural response to a vibratory input interpreted by the patients as if vibration were applied in front of them, rather than laterally. This would correspond to a wrong central interpretation of the input signal. In these otherwise ‘insensitive’ patients, therefore, vibration appears to have some postural effects on the sagittal plane. Since these patients were not those with the head turned most, the wrong interpretation would not depend on the mechanisms responsible for the abnormal head posture, as shown for other motor functions (Anastasopoulos et al., 1998). In passing, all CD patients had on average a posture slightly but significantly more forward (body pitch) with respect to normals under all the experimental conditions, but more so without vibration, perhaps in the search for a ‘safer’ posture, as occurs in normals on closing the eyes (Schieppati and Nardone, 1991; Schieppati et al., 1994) or in spastic patients (Nardone et al., 2001).

Reference frame for spatial orientation

The vibration effect on body orientation would be related to the capacity of the neck proprioceptive input (in this case an asymmetric lateralized input) to modify coherently the egocentric body-centred coordinate system that allows us to estimate our body position with respect to the environment. The vibration-induced input from one SCM muscle would mimic head rotation toward the vibrated side, since during head turning to one side it is the ipsilateral SCM which is being lengthened passively, while the muscle opposite to the rotation direction contracts and shortens (Mazzini and Schieppati, 1992). The tonic neck afferent signals thus elicited would converge onto central networks and give an estimation of the head and trunk posture. In fact, the imbalance of neck proprioceptive inputs can modify the ‘representation’ of the spatial orientation scheme in the context of whole body control, inducing postural, visual and oculomotor responses (Popov et al., 1999; Bove et al., 2001, 2002).

Normal subjects, who voluntarily rotated the head, showed no significant modification in the body orientation under control or vibration conditions. From this finding, it seems that the tonic afferent input connected with the abnormal head posture is not enough to change the reference frame for orientation, at least during stepping-in-place. Obviously, in the normal subjects, voluntary head turning, as opposed to lateralized vibration, is accompanied by the brain activity connected to the volition to turn the head (or the ‘effference copy’; von Holst and Mittelstaedt, 1950), which can succeed in adapting the reference frame during deliberate maintenance of neck torsion.

In the CD patients, the abnormal spontaneous head posture was ineffective, as was the deliberate rotation in the normal subjects. In the patients, the trunk and the body do not appear to match the vibration-induced sensory input from the neck, or to re-align the trunk to the head, at least during stepping-in-place. Perhaps as a consequence of their abnormal head posture, they simply become less sensitive to neck muscle vibration. Possibly, they have learned to rely less on the proprioceptive sensory input from the SCM (or other neck muscles) for their orientation during their navigation, and rely more for this task on the input from other muscle groups not influenced by the head posture, e.g. the trunk paraspinal muscles (Anastasopoulos et al., 1998; De Nunzio et al., 2003).

These findings do not allow the establishment of whether proprioceptive abnormalities are a cause of the abnormal neck muscle contractions or a consequence of an imbalance in other systems controlling neck movements, e.g. the vestibular system (Bronstein and Rudge, 1986; Mazzini and Schieppati, 1994; Colebatch et al., 1995; Munchau and Bronstein, 2001). On the other hand, neck input shapes the output of the vestibular nucleus and its contribution to posture, gaze and perception (Gdowski and McCrea, 1999, 2000, in the primate). Admittedly, we are not in the position to interpret the ‘insensitivity’ to vibration in these patients in the light of any possible subclinical vestibular deficit or of the abnormal interaction between proprioceptive neck and (normal) vestibular input. Perhaps, on the basis of a recent suggestion of Anastasopoulos et al. (2003), the abnormal response to lateral neck vibration in CD patients can be explained as the consequence of an offset of a non-sensory set point signal in the neck proprioceptive loop for head-on-trunk control. It is also difficult to draw conclusions from one snapshot of a population of patients with a different natural history of disease. We can only note that the mean disease duration of the INS group (12.4 ± 6.1 years) was longer than that in the RIGHT and LEFT groups (RIGHT, 7.3 ± 6.1 years; LEFT, 7.3 ± 3.5 years), while the mean age was not different in the three groups.
Conclusions
One may hypothesize that the reference system used in the control of body orientation in space by the CD patients during a locomotor task is refractory to proprioceptive lateral input from the neck or that the input has been re-addressed or biased, whereby the vibration to both sides produces an orientation shift in the same sense. This refractoriness or distortion would be either primitive, connected to the pathogenesis of the disease, or the result of an adaptive process, whereby the proprioceptive input from muscles having an abnormal length or tone is being progressively cancelled. If anything, it seems that this refractoriness increases and occupies both sides with the progress of the disease. This phenomenon might also entrain a slow shift from a reference system based on the head position to a more reliable reference based on another part of the body, such as the trunk; in this process, head posture control is obviously lost.

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References

Proprioception and orientation in dystonia 2777


