Thalamic Single Neuron Activity in Patients With Dystonia:
Dystonia-Related Activity and Somatic Sensory Reorganization


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INTRODUCTION

Dystonia is a movement disorder characterized by sustained muscle contractions leading to twisting movements and abnormal postures (Fahn 1988). There is indirect evidence that neuronal activity in a cerebellar relay nucleus of the human thalamus (ventral intermediate, Vim) and in a pallidal relay nucleus (ventral oral posterior, Vop) is related to dystonic movements. Lesions in Vim and Vop can relieve dystonia (Andrew et al. 1983; Cardoso et al. 1995; Cooper 1976; Gros et al. 1976; Laitinen 1970; Tasker et al. 1988), and stimulation of Vim and Vop can increase dystonia (Tasker et al. 1982) or decrease dystonic movements (Benabid et al. 1996). The effects of thalamic lesioning and stimulation may be related to abnormalities in sensory processing observed in the CNS (Reilly et al. 1992; Tempel and Perlmutter 1990, 1995). These results suggest that thalamic activity is related to dystonic movements.

The characteristics of dystonic movements have not previously been studied quantitatively, but descriptive studies show slow variation of electromyographic (EMG) activity and cocontraction of antagonists around a joint during spontaneous or movement-evoked dystonia (Marsden and Rothwell 1987; Yanagisawa and Goto 1971; Yanagisawa et al. 1972). Rapid phasic bursts also are reported in individual muscles or in both agonists and antagonists together (Cohen and Hallett 1988; Rothwell et al. 1983; Yanagisawa and Goto 1971). Because EMG activity in dystonia is variable, thalamic neuronal and EMG activity must be studied together to understand the relationship of neuronal activity to dystonia.
The purpose of the present study was to test the hypothesis that thalamic activity contributes to dystonic movements. We investigated thalamic neuronal signals and EMG activity recorded during surgical procedures for the treatment of dystonia. We found altered spontaneous activity in Vop and somatic sensory reorganization in Vvm of dystonia patients, findings that suggest a model for the mechanism of dystonia. A preliminary report has been published (Zirn et al. 1998).

METHODS

The operative, physiological, and analytic procedures are outlined briefly because they have been described in previous publications (Lenz et al. 1988a–c, 1990, 1993).

Operative procedures

Observations were made during the physiological exploration preceding either stereotactic thalamotomy for treatment of dystonia or tremor or the implantation of deep brain stimulating electrodes for treatment of chronic pain. During the first stage, the Leksell stereotactic frame was applied and the coordinates of the anterior commissure-posterior commissure (AC-PC) line were determined. Neuronal activity in the thalamus was recorded with a high-impedance microelectrode (Lenz et al. 1988a,b). The first electrode trajectory was directed toward the principal somatic sensory nucleus (ventral caudal, Vc), the most reliable landmark for the exploration. Subsequently the region anterior to Vc was mapped by analysis of both single neuron activity and effects of microstimulation (Lenz et al. 1988a).

During neuronal recordings, we examined the spontaneous firing pattern, the relationship of spontaneous activity to dystonia, and the neuronal activity during somatic sensory stimulation and active movement. Cutaneous sensory cells responded to touch or pressure to the skin. Deep sensory cells responded to joint movement and/or squeezing of muscles or tendons in the absence of any response to stimulation of skin deformed by these stimuli. Care was taken to isolate movements to single joints.

Microstimulation was delivered in trains of ~1-s duration at 300 Hz by using biphasic pulses consisting of a 0.2-ms anodal pulse followed in 0.1 ms by a 0.2-ms cathodal pulse of the same magnitude. At each stimulation site, the patient was asked to elevate his/her arm, and the effect of the stimulation on dystonia was assessed. Additionally, patients were asked to describe stimulation-evoked sensations using a standard protocol (Lenz et al. 1993, 1994a). If any effect was observed, then a threshold was determined for the effect (threshold microstimulation, TMIS) (Lenz et al. 1993).

The lesion site in patients with dystonia was located anterior to the principal sensory nucleus (Vc) where the majority of cells responded to cutaneous stimulation. Lesion sites were chosen in regions where cells displayed activity related to dystonic movements and where microstimulation evoked changes in the dystonic movements. Lesions were made by using a radiofrequency lesioning electrode with an outside diameter of 1.1 mm and an exposed length of 3 mm (TM electrode, Radionics, Burlington, MA). A neurological examination to evaluate pyramidal tract function, cutaneous sensation, speech, and cerebellar function was carried out before, during, and after each stage of lesion making. Lesions were made in two stages, with the temperature of the electrode held at 70°C for 1 min and then at 80°C for 1 min.

An egg white test was carried out to estimate the size of the lesion made by this technique (Cosman and Cosman 1985). The electrode was suspended in egg white maintained at 37°C, and a lesion was made as described in the preceding text. The resulting coagulum was measured with calipers. The coagulum approximated a cylinder with a diameter of 3 mm (2.8 ± 0.1 (SD) mm, n = 5) and a length of 5 mm (4.9 ± 0.1) (Lenz et al. 1995). Lesions of this size compare favorably with those measured by others using a similar electrode (Cosman and Cosman 1985).

Movement paradigm and assessment

Dystonic movements occurred spontaneously in the upper limb in all patients and increased when the patients elevated the arm. Patients were seated in a reclining position with the back tilted 20° above the horizontal. Patients then were asked to point toward the ceiling (arm elevated). This action flexed (45°) and abducted the shoulder (90°) and extended the elbow, wrist, metacarpophalangeal, and interphalangeal joints (~160°). Neuronal activity was assessed for 20–60 s with the arm in this position. The activity of a subpopulation of cells (15 cells in 3 patients) was assessed with the arm in two separate positions, elevated and at rest. Throughout the analysis differences in these two positions were compared statistically for this subpopulation.

Thalamic neuronal activity was recorded as previously described (Lenz et al. 1988b). Standard techniques were used to record EMG activity in wrist flexors, wrist extensors, biceps, and triceps (Lenz et al. 1988c). EMG activity in deltoid was not monitored because dystonia, either at rest or during pointing, always involved elbow and wrist more than shoulder. Neuronal and EMG signals were recorded on a multiple channel tape recorder (Model 4000, Vetter, Rebersburg, PA). An audio channel recorded a description of the procedure, and another channel recorded the signal from a foot pedal, indicating the duration of somatic sensory stimuli.

Analytic procedures

Tape-recorded neuronal and EMG activities were examined postoperatively. The present report focuses on single neuron activity recorded in the region where cells exhibited activity related to active or passive movements of the upper extremity (Lenz et al. 1990). Action potentials were discriminated by amplitude (D-DISI, Bak Electronics, Rockville, MD) and confirmed to arise from a single cell. The confirmation criterion was constant shape of the action potential as verified by displaying the shape on a storage oscilloscope. Times of occurrence of discriminated action potentials were stored at a clock rate of 1,000 Hz. EMG signals were digitized at a rate of 200 Hz on a digital computer (11/73, Digital Equipment). The data were analyzed on a workstation (DECstation 3100, Digital Equipment) with SAS, version 6.

Figure 1 shows an example of simultaneously recorded thalamic and EMG activity in a patient with dystonia. Both thalamic and EMG signals varied slowly at about the same frequency and increased at 4 s and possibly at 6 and 7.5 s. Visual examination of the spike and EMG signals, however, is inadequate to assess either the composition of or the correlation between the spike and EMG signals. Therefore thalamic and EMG signals were analyzed in the frequency domain. The spike train was converted into an equivalent analog signal by use of the French-Holden algorithm (French and Holden 1971; French et al. 1972; Glaser and Ruchkin 1976; Lenz et al. 1988c). The EMG signal first was processed to eliminate movement artifact by band-pass filtering (~6 dB below 20 Hz and above 120 Hz). The envelope of EMG activity then was produced by full-wave rectification and filtering (~6 dB above 20 Hz). The 10% cosine rule then was applied to eliminate low-frequency components generated by finite sampling of the signals (Glaser and Ruchkin 1976).

Standard techniques used to take the spectrum of these two signals resulted in 256 estimates of the spectrum between 0 and 25 Hz (Bendat and Piersol 1976; Glaser and Ruchkin 1976; Lenz et al. 1988c; Oppenheim and Schafer 1975). Cross-correlation spectral analysis (Fig. 1, B–D) was carried out to determine whether the two signals were correlated. The raw power spectra are shown in Fig. 1, B and C, left (resolution, 0.1 Hz). In Fig. 1, B and C, right,
eight contiguous, nonoverlapping spectral estimates are averaged to produce smoothed spectral estimates (resolution, 0.78 Hz). Smoothed spectra give a more statistically reliable estimate but at a cost of decreased resolution (Glaser and Ruchkin 1976).

The coherence function was evaluated as a measure of the probability that two signals were related linearly. The coherence had a value of 0 if the spike and EMG signals were not linearly related and a value of 1 if the two had a perfect linear relationship (Bendat and Piersol 1976; Glaser and Ruchkin 1976; Lenz et al. 1988c; Oppenheim and Schafer 1975). A coherence of 0.42 at a given frequency indicated that the two signals were likely (P < 0.05) to be related linearly at that frequency (Benignus 1969). The signals in Fig. 1 were coherent in the lowest frequency band as indicated by a coherence of 0.5. Phase was calculated by standard techniques (Bendat and Piersol 1976; Glaser and Ruchkin 1976; Lenz et al. 1988c; Oppenheim and Schafer 1975) so that a negative phase for the cross-correlation function spike X EMG indicated that the spike signal was phase advanced on the EMG signal. The phase of the spike X EMG function at the frequency of dystonia in Fig. 1 was −100°, which indicated that the spike train was phase advanced on the EMG signal.

**RESULTS**

The patient population included 10 patients with dystonia undergoing thalamotomy for treatment of the disorder (see Table 1). In accord with accepted definitions, dystonia was classified as either primary and secondary (Fahn 1988). Primary dystonia was either familial or sporadic and was characterized by the absence of an identifiable underlying cause. Secondary dystonia was caused by a specific disease or lesion. Secondary dystonia affecting the upper and lower extremity on the same side was termed hemidystonia. All patients selected for surgery had disabling distal upper extremity dystonia, characterized by twisting movements rather than sustained postures.

For studies of thalamic dystonia-related activity the control population consisted of five patients (referred to as “controls with pain”) undergoing implantation of deep brain stimulating electrodes in the thalamus for treatment of deafferentation pain. Four of these patients had a complete and one an incomplete thoracic spinal cord transection. None had motor or
sensory abnormalities involving the upper extremity. For the study of EMG activity, the four control subjects (referred to as “normal controls”) were normal by neurological history and examination.

Comparisons between dystonia patients and controls are of interest, although they are constrained by limitations of human intraoperative studies. In dystonia patients, all cells were studied during pointing, and a subpopulation of cells was studied during pointing and with the arm at rest. In this subpopulation, spike data were similar during pointing and with the arm at rest. In controls with pain, cells were studied with the arm at rest. Spike data in dystonia patients (83 cells, 19 electrode trajectories) were compared with that in controls with pain (59 cells, 11 electrode trajectories).

**EMG signal**

**CHARACTERISTICS OF EMG POWER IN DYSTONIA.** Studies of EMG signals in dystonia focused on spectral composition of these signals and the degree to which different EMG channels were cross-correlated. A linear relationship between two signals was explained most easily if the two signals had a similar spectral composition (Bendat and Piersol 1976; Glaser and Ruchkin 1975). Therefore the spectral composition of EMG activity first was studied as a basis for interpreting the spectral composition of thalamic signals. Because thalamic activity was to be analyzed relative to multiple EMG channels, we analyzed the degree to which different EMG channels were cross-correlated with each other. After studies of spectral composition and cross-correlation of EMG channels, we analyzed the relationship between thalamic and EMG signals.

The pattern of EMG activity during pointing was much different in dystonia patients (Fig. 1A) than in normal controls (Fig. 2). Figure 2 shows the raw signal and smoothed spectrum for one epoch of EMG activity in a normal control. Note that the slow modulation of the EMG signal (shown in Fig. 1A) and the low-frequency EMG autopower peak in dystonia patients (Fig. 1C) was not seen in normal controls (Fig. 2). This difference between dystonia patients and normal controls was borne out by the spectral analysis of these signals across patients (Fig. 3).

Analyses of EMG activity during dystonia were carried out for 67 epochs recorded in patients A–C, and H (Table 1) and 24 epochs recorded in four normal controls. Figure 3 (top 4 rows) illustrates the frequency of peak EMG power observed in dystonia patients. In the cell population studied with the patient’s arm elevated (Fig. 3, n = 67 epochs), the peak EMG activity occurred in the lowest frequency band (mean, 0.39 Hz; range, <0.78 Hz) in the majority of epochs in all muscles studied. The only exception was that the biceps of patient C had a significantly higher peak EMG frequency (Bonferroni t-test P < 0.0001) than did other EMG channels and other patients (nested ANOVA by patient and EMG channel, F = 7.6, df = 9, P < 0.0001). This high-frequency activity was related to dystonic tremor of the elbow observed in this patient (Tolosa and Marti 1997; Yanagisawa et al. 1972). Even in this patient, 45% of epochs had biceps peaks in the lowest frequency band (mean, 0.39 Hz, range, <0.78 Hz) in the majority of epochs in all muscles studied. The only exception was that the biceps of patient C had a significantly higher peak EMG frequency (Bonferroni t-test P < 0.0001) than did other EMG channels and other patients (nested ANOVA by patient and EMG channel, F = 7.6, df = 9, P < 0.0001). This high-frequency activity was related to dystonic tremor of the elbow observed in this patient (Tolosa and Marti 1997; Yanagisawa et al. 1972). Even in this patient, 45% of epochs had biceps peaks in the lowest frequency range, and all other channels had peak power in the lowest frequency band for most epochs. For the subpopulation (n = 15 epochs) studied in two arm positions (pointing and at rest), no significant difference in the frequency of peak EMG power was found as a function of arm position or muscle group (2-way ANOVA, F = 1.8, P > 0.1).

Figure 3, bottom, shows the peak EMG power, displayed for all epochs in normal controls. Peak activity in all channels most frequently occurred between 5 and 25 Hz and was rarely in the lowest frequency band (dystonia frequency). In normal controls, the frequency of peak EMG did not occur at the same frequency range.
frequency in different EMG channels for any epoch studied. During pointing in normal controls, the difference in the frequency of peak EMG between channels and the high frequency of EMG activity may reflect the characteristic firing frequencies of motor neurons recorded from different channels (Henneman and Mendell 1981).

In summary, peak EMG activity was dominated by activity in the lowest frequency band in patients with different etiologies of dystonia (cf. biceps in patient C). In normal controls, EMG activity rarely occurred in the lowest frequency band during pointing. We concluded that peak activity in the lowest frequency band was a characteristic feature of EMG activity in dystonia, regardless of etiology (Table 1). Consequently, our study focused on the lowest frequency band (dystonia frequency) because it contained peak EMG activity for the majority of epochs in all 10 dystonia patients.

ANALYSIS OF SIMULTANEOUS CONTRACTION. To assess the degree to which muscles were contracting simultaneously, we performed cross-correlation analysis between pairs of muscles throughout the upper extremity (Fig. 4). Simultaneous contraction of muscle pairs was defined by EMG peaks at dystonia frequency with coherence $>0.42$ and phase difference less than $30^\circ$. Simultaneous contraction of antagonistic muscles (co-contraction) occurred in 63% (42/67) of epochs for antagonists about the wrist and 39% (26/67) of epochs for antagonists about the elbow. Differences between patients in the proportions of epochs showing simultaneous contraction were not significant for antagonists about the elbow ($P > 0.09$, $\chi^2$) or wrist ($P > 0.3$, $\chi^2$), a finding that suggests cocontraction was not a function of the etiology of dystonia (Table 1).

Simultaneous contraction was found in 45% (30/67) of epochs for flexor pairs (wrist flexors X biceps) and 31% (21/67) of epochs for extensor pairs (wrist extensors X triceps). Simultaneous contraction also was found for crossed muscle pairs: 28% (19/67) of epochs for wrist flexors X triceps and 21% (14/67) of epochs for wrist extensors X biceps. These correlations were not due to cross-talk between EMG channels because the higher frequency components of the EMG signals were rarely coherent. Therefore analysis of the EMG signal in patients with dystonia indicated that there was a concentration of power in the lowest frequency band (dystonia frequency) with simultaneous contraction of multiple muscle pairs.

**Thalamic spike signal**

NEURONAL LOCATION. Because neuronal properties may vary between nuclei, neuronal location was considered before details of neuronal activity were studied. In human studies mapping this area, the anterior border of Vc usually is estimated from the most anterior cell in the region where the majority of cells respond to either deep or cutaneous stimulation (Lenz et al. 1990, 1994c). This distinguishes Vc from Vim, where deep sensory cells are less common. This border was poorly defined in dystonia patients because of the high density of deep sensory cells in presumed Vim in many of these patients (Figs. 5 and 7). For this reason, the physiological map was shifted along the AC-PC line until the most anterior cell responding to cutaneous
stimulation was at the anterior border of Vc. The borders of presumed Vim and presumed Vop were determined from this transformed map.

This method of estimation included a systematic error: Vc did not include the anterodorsal shell of this nucleus, which contained cells responding to deep sensory inputs (Friedman and Jones 1981; Jones et al. 1982; Lenz et al. 1990). Human histological studies have suggested that the anterodorsal shell region extends ~1 mm anterior to the anterior border of the cutaneous core of Vc (Figure 20 in Hirai and Jones 1989a). However, we could not locate the anterodorsal shell region accurately because there is no human atlas that defines the boundaries of this region. This method of estimation was used as a reasonable first approximation of nuclear location within the constraints imposed on studies in humans.

<table>
<thead>
<tr>
<th>MEAN INTERVALS IN PATIENTS WITH DYSTONIA AND IN CONTROLS WITH PAIN.</th>
<th>Patient B</th>
<th>Patient H</th>
<th>Patient C</th>
<th>Patient A</th>
<th>Normal controls (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist Flexor</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
</tr>
<tr>
<td>Wrist Extensor</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
</tr>
<tr>
<td>Biceps</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
</tr>
<tr>
<td>Triceps</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
<td>[75]</td>
</tr>
</tbody>
</table>

FIG. 3. Histograms of occurrence of peak EMG power at different frequencies during pointing in patients with dystonia (top 4 panels) and in normal controls (bottom). Note that the EMG activity across muscles and patients occurs in the lowest frequency band (<0.78 Hz) commonly in dystonia patients but uncommonly in normal controls.

MEAN INTERVALS IN PATIENTS WITH DYSTONIA AND IN CONTROLS WITH PAIN. We first compared basic properties of the spike train among patients with dystonia. Differences in mean interspike intervals (ISIs) among these patients were not significant (1-way ANOVA, $F = 2.38$, $df = 3$, $P > 0.07$), suggesting that the firing rate of spontaneous activity during dystonia was not related to etiology. In dystonia patients, spontaneous neuronal activity during pointing was recorded for all cells; some cells were studied both during pointing and at rest, but no significant difference (1-way ANOVA $F = 0.50$, $df = 1$, $P > 0.4$) in the mean ISI was found between the two positions. Thalamic firing rates in patients with dystonia were thus independent of arm position and could be compared with those of the control population with the arm at rest. Table 2 lists mean ISIs for thalamic neurons in dystonia patients and in control patients with pain. Populations of neurons also were grouped by nuclear location (row A) and the presence of sensory input (row B).

ISIs were longer for the cells recorded in presumed Vim and presumed Vop of patients with dystonia than for those cells in controls with pain (Table 2, rows A and C). With the arm at rest, ISIs were longer ($P < 0.05$, $t$-test) in dystonia patients [0.103 ± 0.015 (SE) s] than in controls (0.072 ± 0.009 s). ISIs also were significantly ($P < 0.01$, $t$-test) longer in patients with dystonia during pointing (0.11 ± 0.012 s) than in controls with the arm at rest (0.073 ± 0.12 s). A two-by-two ANOVA of ISIs carried out by nuclear location (presumed Vim or presumed
and patient type (dystonia patient/control) indicated significant differences ($F = 3.4, \text{df} = 3, P < 0.03$). Post hoc analysis of neurons in presumed Vim showed that the cells in dystonia patients had significantly longer ISIs than did those in the control population (1-way ANOVA, $F = 6.7, \text{df} = 1, P < 0.02$). ISIs in presumed Vop tended to be longer in patients with dystonia than in the controls with pain, although the results did not reach significance (1-way ANOVA, $F = 2.2, \text{df} = 1, P < 0.15$), perhaps because of the small number of cells ($n = 9$) studied in the control population. These results indicate that cells in presumed Vim fired at lower rates in dystonia patients than in controls. Differences in mean ISI also were studied for neurons that responded to deep sensory stimulation (deep sensory cells) and those that did not (nonsensory cells). Both the deep sensory and nonsensory cell groups in patients with dystonia tended ($F = 2.5, \text{df} = 3, P < 0.06$) to have longer ISIs than did these cells in control patients (Table 2, row B). ISIs were significantly (2-way ANOVA, $F = 2.9$,
df = 3, \( P < 0.04 \)) longer for nonsensory cells in dystonia patients than in control patients (Table 2, row C). Post hoc testing revealed that nonsensory cells in presumed Vim had significantly longer ISIs in dystonia patients than in the control population (1-way ANOVA, \( F = 5.5, \text{df} = 1, \ P < 0.02 \)). The same trend was seen for nonsensory cells in presumed Vop, although differences did not reach significance (1-way ANOVA, \( F = 2.0, \text{df} = 1, \ P < 0.2 \)). These results indicate that nonsensory cells in presumed Vim consistently fired at lower rates in dystonia patients than in control patients.

**Table 2. Interspike intervals for different populations of cells in patients with dystonia and controls with pain**

<table>
<thead>
<tr>
<th>Cell Population</th>
<th>Dystonia</th>
<th>Controls With Pain</th>
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<tbody>
<tr>
<td>A</td>
<td>( \text{Presumed Vim} )</td>
<td>( 0.12 \pm 0.013 \text{ s} )</td>
</tr>
<tr>
<td></td>
<td>( n = 57 )</td>
<td>( n = 49 )</td>
</tr>
<tr>
<td>B</td>
<td>( \text{NS} )</td>
<td>( 0.087 \pm 0.012 \text{ s} )</td>
</tr>
<tr>
<td></td>
<td>( n = 21 )</td>
<td>( n = 9 )</td>
</tr>
<tr>
<td>C</td>
<td>( \text{NS} )</td>
<td>( 0.13 \pm 0.017 \text{ s} )</td>
</tr>
<tr>
<td></td>
<td>( n = 34 )</td>
<td>( n = 40 )</td>
</tr>
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</table>

**CHARACTERISTICS OF SPIKE POWER.** In dystonia patients, the peak spike activity usually occurred at dystonia frequency (Fig. 6). The proportion of neurons with peak activity at dystonia frequency was significantly higher (\( P < 0.005, \chi^2 \)) in patients with dystonia than the proportion in controls with pain. For the subpopulation of cells studied during pointing and with the arm at rest in dystonia patients, the average frequency of peak spike power did not vary significantly (\( F = 0.68, \text{df} = 1, \ P > 0.4 \)) between the two positions. Therefore with the arm elevated or at rest, peak activity at dystonia frequency was much more common in dystonia patients than in controls with pain.

One patient (patient C, Fig. 3) had high-frequency biceps EMG activity consistent with his clinically evident dystonic tremor (Tolosa and Marti 1997; Yanagisawa et al. 1972). Spike peaks in the patient with dystonic tremor often occurred at the

**FIG. 5.** Map of neural activity in and anterior to nucleus ventral caudal (Vc) in patient C. Top: locations of stimulation/recording sites relative to the anterior-posterior commissure (AC-PC) line indicated by the horizontal line. PC is located at the right end of the line. Electrode trajectories (P4 and P5) are shown by the 2 oblique lines. Locations of recording sites are indicated by ticks to the left. All sites are numbered sequentially and numbers are indicated for every 5th tick. Scale as indicated. Panels P4 and P5 show the site number, effect of threshold microstimulation (TMIS), and receptive field (RF). Effect of TMIS at any site is listed below and to the left of the site number. If the evoked effect was a sensation, then a figurine indicating the location of the sensation (projected field, PF) is shown. Threshold current (in \( \mu \text{A} \)) is indicated below the PF figurine. NR, no effect was evoked at that site by stimulation at \# to 80 \( \mu \text{A} \). RF is indicated to the right and below the site number. Note that many cells responded to movement of 2 joints. For example, cells 114 and 120 responded optimally to extension of both fingers and wrist. Shading on the figurine indicates the part of the body where mechanical stimulation-evoked cellular activity. All shaded figurines indicate cutaneous stimulation, except for neurons 86 and 107 at which cellular activity was evoked by manipulation of muscle but not by manipulation of the overlying skin.
frequency of biceps tremor. This patient accounted for most (76%) of the cells in dystonia patients with an SNR peak at >5 Hz (Fig. 6A, right). On statistical testing, significant differences between patients \((F = 5.09, df = 3, P < 0.003)\) were attributable to the difference between patient C \((P < 0.05, \text{SAS general linear models procedure})\) and the mean. In this patient, peak activity was in the dystonia frequency range for 35% of thalamic cells studied, for 65–90% of epochs in upper extremity muscles other than biceps and for 45% of epochs in biceps. Therefore both thalamic and EMG signals in this patient were often at dystonia frequency. Although tremor is associated clinically with dystonia (Yanagisawa et al. 1972), we did not analyze activity in the tremor frequency band because it formed such a small part of our sample.

**POPULATIONS OF CELLS WITH POWER CONCENTRATED IN THE LOWEST FREQUENCY BAND.** Table 3 shows populations of cells having peak spectral power at dystonia frequency and a ratio of power at dystonia frequency to total spectral power (signal-to-noise ratio—SNR) greater than two. The proportion of cells with a dystonia frequency peak of SNR $\geq 2$ was significantly higher \((P < 0.05, \chi^2)\) for patients with dystonia (37/83, 44.6%) than for control patients with pain (15/59, 25.4%). The proportion of nonsensory cells with a dystonia frequency peak of SNR $\geq 2$ was significantly higher in patients with dystonia than in controls \((P < 0.01, \chi^2)\). The proportion of sensory cells with SNR $\geq 2$ was significantly higher in patients with dystonia patients than in controls. These characteristics did not differ significantly \((P > 0.05, \chi^2)\) between these two populations.

**TABLE 3.** Cell populations with a concentration of power (signal noise ratio $\geq 2$) in the spike power peak at dystonia frequency (<0.79 Hz)

<table>
<thead>
<tr>
<th>Cell Population</th>
<th>Dystonia</th>
<th>Control</th>
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<tbody>
<tr>
<td>A Sensory (NS)</td>
<td>6/25 (24.0)</td>
<td>1/9 (11.1)</td>
</tr>
<tr>
<td>B Sensory (NS)</td>
<td>31/58 (53.5)</td>
<td>14/50 (28.0)</td>
</tr>
<tr>
<td>C Presumed Vop (NS)</td>
<td>17/21 (81.0)</td>
<td>0/9 (0.0)</td>
</tr>
<tr>
<td>D Sensory in presumed Vim (NS)</td>
<td>5/23 (21.7)</td>
<td>1/9 (11.1)</td>
</tr>
<tr>
<td>E Nonsensory cells in presumed Vop (NS)</td>
<td>13/34 (38.2)</td>
<td>14/40 (35.4)</td>
</tr>
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</table>

Proportions were tested by $\chi^2$ or Fisher exact test as appropriate. Values in parentheses are percentages.

Spike X EMG function in patients with dystonia

The spike X EMG coherence did not vary significantly between muscles (1-way ANOVA, $F = 0.92, df = 3, P > 0.4$) nor did spike X EMG functions differ substantially between a single cell and each of the four muscles studied. Eleven cells had significant spike X EMG coherence at dystonia frequency for two of the muscles studied. Three cells had significant spike X EMG coherence for three muscles, and two cells had significant spike X EMG coherence for all four of the muscles studied. For 81% (13/16) of these cells, maximal differences in spike X EMG coherence between different EMG channels were not significant. These results demonstrate that peak spike power of nonsensory cells in Vop, but not in Vim, is concentrated at dystonia frequency more commonly in patients with dystonia than in controls.

**FIG. 6.** Histograms of occurrence of Spike power peak activity at different frequencies during dystonia. Thalamic spike activity is shown for cells recorded in 4 different dystonia patients (A) and controls with pain (B). Note that peaks in the lowest frequency band occur more frequently in dystonia patients than in controls with pain.
bility, we analyzed coherence in the subpopulation of cells studied during pointing and with the arm at rest. There was no significant difference by arm position and muscle group in the spike X EMG coherence (2-way ANOVA, $F = 0.60$, df = 7, $P > 0.75$). The difference in phase could not be statistically tested because of the small number of cells with interpretable phase (i.e., spike X EMG coherence $>0.42$). These results suggested that thalamic activity, EMG activity, and the relationship between them were independent of arm position in patients with dystonia.

Spike X EMG as a function of location in presumed Vim or presumed Vop

The spike X EMG function at dystonia frequency was examined for both presumed Vim and presumed Vop. This analysis showed no significant difference ($P > 0.05$, $\chi^2$) in the percentage of cells having spike X EMG coherence $>0.42$ between presumed Vim (range for the 4 EMG channels: 28–46%) and presumed Vop (range: 13–23%) for any of the four EMG channels, perhaps due to the small sample. Thus there was no significant difference between presumed Vim and presumed Vop in the proportion of cells correlated with EMG activity.

The number of spike X EMG pairs showing negative phase was examined separately for each EMG channel. The proportion of cells with a negative phase for any EMG channel was the same ($P > 0.05$, $\chi^2$) in presumed Vim (range of percentages for the 4 EMG channels: 50–83%) and presumed Vop (range: 66–100%). Thus spike activity was phase advanced on EMG activity in dystonia for most spike X EMG functions in both presumed Vim and presumed Vop. Differences between EMG channels were not significant.

Thalamic somatic sensory activity

For studies of somatic sensory activity, the control group was enlarged to allow statistical comparisons. This group (referred to as “controls with pain or tremor”) consisted of patients undergoing thalamotomy for the treatment of essential tremor (2 patients), cerebellar tremor (4 patients), and tremor in Parkinson’s disease (3 patients), in addition to the five patients with chronic pain. The patients with Parkinson’s disease had the tremor predominant variant, with tremor and cogwheel rigidity but no dystonia and minimal bradykinesia (Paulson and Stern 1997).

A total of 38 electrode trajectories were made in the dystonia patients and 43 in the controls with pain or tremor. All electrode trajectories in a patient were separated by $\geq 2$ mm. Neuronal recordings were made from 483 cells in the region of presumed Vim and presumed Vop of patients with dystonia and from 412 cells in the controls. The target for the surgery was Vc in patients with pain (Hosobuchi 1986), Vim in patients with tremor (Lenz et al. 1995), and Vim/Vop in patients with dystonia (Bertrand and Lenz 1995). Therefore the exploration in controls with pain or tremor was biased toward Vc and Vim, whereas the exploration in dystonia patients was biased toward Vop and Vim. To correct for the differences in sampling of Vc, presumed Vim, and presumed Vop by patient population, neuronal results are reported by nucleus.

Somatic sensory activity

ANATOMIC DISTRIBUTION. Figure 5 shows a dystonia patient’s map of the thalamus with nuclear location shifted to align the anterior border of Vc with the location of the most anterior cutaneous sensory cell. Numerous cells in the region anterior to Vc were classified as deep sensory cells. This figure illustrates the large area in which cells respond to movements of the wrist (P5, 116–121, and P4, 72–78). Many of these cells (site numbers 79, 111, 114, 120, 122, and 123) responded to movements of more than one joint. The number of deep sensory cells responding to movement of more than one joint was significantly higher in patients with dystonia (26%, 13/52) than in control patients (8%, 4/49; Fisher exact, $P < 0.05$).

In Fig. 7, the locations of cells from different patients are displayed relative to presumed Vim and presumed Vop (transformed as earlier described in NUCLEAR LOCATION) for control patients with pain or tremor (left, $n = 8$) and for patients with dystonia (right, $n = 10$). Deep sensory cells are present in presumed Vim and presumed Vop of both groups of patients. This finding is consistent with several recent studies in the corresponding nuclei, ventral posterior lateral pars oralis (VPLo) and ventral lateral pars oralis (VLo) (Hirai and Jones 1989a), in awake monkeys (Anderson and Turner 1991; Butler et al. 1992; Vitek et al. 1994a) but not with all studies in anesthetized monkeys (Friedman and Jones 1981; Jones et al. 1982). Because sampling of cells in the region of presumed Vim and presumed Vop in controls and in patients with dystonia differed, the sensory properties of cells in these populations were compared by nucleus.

Electrode trajectories through presumed Vim and presumed Vop (Fig. 7) in some dystonia patients had a high density of deep sensory cells, whereas trajectories in other patients did not. The proportion of deep sensory cells was not explained by clinical characteristics of the dystonia patients. Because of the large variance among patients, there was no significant difference ($t$-test, $P > 0.05$) between the percentage of deep sensory cells in presumed Vim and presumed Vop between patients with primary dystonia (percentage per individual patients: 0, 6, 11, and 48%) and secondary dystonia (0, 13, 61, and 67%, see Fig. 5). Neither did the percentage of deep sensory cells in presumed Vim and presumed Vop ($r = 0.46, P > 0.05$) correlate with the duration of dystonia. Sampling bias, particularly in the location of trajectories with respect to the thalamic somatotopy, might explain the differences between patients.

Table 4 shows that the proportion of deep sensory cells in presumed Vim was significantly higher ($P < 0.01, \chi^2$) in dystonia patients than in controls. Differences in presumed Vop followed the same trend but did not reach significance ($P < 0.15, \chi^2$). Presumed Vim contained a significantly greater ($P < 0.01, \chi^2$) proportion of deep sensory cells (28%) than did presumed Vop (11%) in dystonia patients but not in controls ($P > 0.05$, Fisher exact). No significant differences were found between the proportions of cells with deep somatic sensory responses in Vim or presumed Vop ($\chi^2$, $P > 0.05$) of individual patients with tremor of Parkinson’s disease, essential tremor, cerebellar tremor, or chronic pain. The proportion of deep sensory cells thus was consistently higher in presumed Vim and presumed Vop of patients with dystonia than in that of controls.
THALAMIC REORGANIZATION IN DYSTONIA. In addition to the increased percentages of deep sensory cells, there was an apparent increase in the size of the representation of individual joints in presumed Vim of patients with dystonia. For example, passive wrist movements were represented over a distance of 3.2 mm in electrode trajectory P4 of patient C (see Fig. 5, sites 72–78). Detailed mapping of the two- or three-dimensional extent of the representation of deep structures could not be justified clinically, although it is the standard in monkey studies. For this reason, the maximum size of the representation of deep RFs in the controls with pain and tremor and patients with dystonia. Site location is shown relative to the AC-PC line (nearly horizontal lines) and nuclear boundaries, as estimated from the position of the AC-PC line. Top 2 panels: results pooled for planes between 13.0 and 14.5 mm lateral to the midline (labeled 13.5). Middle 2 panels: pooled results recorded for planes between 14.5 and 15.9 mm lateral to the midline (labeled 15.0). Bottom 2 panels: results for electrode trajectories located >15.9 mm lateral to the midline (labeled 16.5). Electrode trajectories were translated along the AC-PC line so that the most anterior cell responding to cutaneous stimulation in that patient was located at the anterior border of Vc.
A part of the body was estimated from the lengths of single electrode trajectories along which all RFs included a single joint as in a previous study (Lenz et al. 1994b). We restricted our analysis to the wrist or elbow representation to target the thalamic area in which these joints are represented (Lenz et al. 1988b, 1990). The bias toward this representation is indicated by the incidence of RFs, which included the wrist or elbow joint for 79% of all deep RFs in dystonia patients.

It is possible that long electrode trajectory lengths with cellular RFs including one joint might be compensated for by shorter lengths along adjacent electrode trajectories. However, the pair of electrode trajectories in Fig. 5 had constant RFs over a substantial length of each of the two. Furthermore, the differences between adjacent electrode trajectories would be expected to be similar for dystonia and control patients because the mapping techniques were the same. We believe, therefore, that statistical comparison of these two populations is valid.

We plotted electrode trajectory lengths over which all RFs included a single joint, either wrist or elbow (Fig. 8). Cells having RFs with multiple joints were excluded because this might increase electrode trajectory lengths with a constant RF. Lengths of electrode trajectories were measured by nucleus. If an electrode trajectory traversed the border between Vim and Vop, then the lengths within either nucleus were measured separately and assigned to the appropriate nucleus. Lengths of electrode trajectories through motor thalamus (including both presumed Vim and presumed Vop) with constant deep RFs were significantly longer among dystonic patients than among the controls ($P < 0.03$, Kurskal-Wallace ANOVA by ranks). If results were analyzed for each nucleus separately, electrode trajectories in Vim with a constant RF tended to be longer in dystonic patients than in controls ($P < 0.055$, Kurskal-Wallace ANOVA). The same trend apparently applied in Vop (Fig. 8), although the number of data points was too small to test statistically.

### Spike X EMG functions for sensory and nonsensory cells

The correlation between thalamic and EMG activity was studied to examine the mechanism by which sensory cells influenced dystonia. At dystonia frequency, the proportion of cells with coherence $>0.42$ for one spike X EMG function did not differ significantly ($P > 0.05$, $\chi^2$) between nonsensory cells (range for EMG channels 1–4: 25–32%; $n = 58$ cells) and sensory cells (range: 0–60%; $n = 25$) for any EMG channel. Differences between the number of sensory and nonsensory cells showing phase $<0$ were assessed for each EMG channel separately. This analysis showed no significant difference ($P > 0.05$, Fisher exact test) in the percentage of sensory cells having spike X EMG phase $<0$ (range for the 4 EMG channels: 0–100%) and the percentage of nonsensory cells (range: 40–100%) for any of the four EMG channels. Overall, sensory and nonsensory cells were equally likely to be correlated with and to lead EMG activity.

### Spike X EMG functions of individual sensory cells

We next examined the spike X EMG function for the EMG channel appropriate to the neuronal RF for sensory cells in Vim and Vop. As a first approximation, the effector muscle of a thalamic neuron was defined as the muscle that, by contraction, caused a joint movement that produced a sensory discharge when the joint was passively moved by the examiner. For example, biceps would be the effector muscle for a cell that discharged when the examiner flexed the elbow. In the present study, noneffector muscles were

![FIG. 8. Lengths of electrode trajectories along which all cells had RFs for a single joint, either the wrist or the elbow.](http://jn.physiology.org/)

<table>
<thead>
<tr>
<th>TABLE 4. Percentages of deep sensory cells in Vim and Vop of patients with dystonia and of the control population (pain and tremor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain and Tremor $(P &gt; 0.05)$, %</td>
</tr>
<tr>
<td>Presumed Vim—A “Cerebellar” Relay $(P &lt; 0.01)$</td>
</tr>
<tr>
<td>Presumed Vop—A “Pallidal” Relay $(P &lt; 0.15)$</td>
</tr>
</tbody>
</table>

The percentage of deep sensory cells found in different thalamic motor nuclei is shown for the dystonic and control populations. Significance of differences in proportions are indicated for each column and row. Number of cells examined are in parentheses.
TABLE 5. Phase of the cross correlation function between sensory cells and EMG activity

<table>
<thead>
<tr>
<th>Cell Number</th>
<th>Movement Producing Increased Cellular Activity</th>
<th>Channels Correlated With Spike Train</th>
<th>Coherence in EMG</th>
<th>Phase, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>210701:1</td>
<td>Wrist flexion (WF)</td>
<td>WE-0.46</td>
<td>+56</td>
<td></td>
</tr>
<tr>
<td>0311401:1*</td>
<td>Wrist extension (WE)</td>
<td>WE-0.84</td>
<td>-15.3</td>
<td></td>
</tr>
<tr>
<td>9302401:4*</td>
<td>Finger extension (WE)</td>
<td>WE-0.46</td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td>0308601*</td>
<td>Finger extension WE-0.59</td>
<td>WE-0.43</td>
<td>-50</td>
<td></td>
</tr>
<tr>
<td>0310901*</td>
<td>Finger extension WE-0.59</td>
<td>WF-0.69</td>
<td>+14</td>
<td></td>
</tr>
<tr>
<td>0311501*</td>
<td>Wrist extension WE-0.43</td>
<td>WE-0.43</td>
<td>-89</td>
<td></td>
</tr>
<tr>
<td>0311601*</td>
<td>Wrist flexion WE-0.74</td>
<td>WF-0.62</td>
<td>-102</td>
<td></td>
</tr>
<tr>
<td>0312101*</td>
<td>Elbow and wrist extension EE-0.42</td>
<td>WF-0.48</td>
<td>-137</td>
<td></td>
</tr>
<tr>
<td>0308902</td>
<td>Finger extension WE-0.42</td>
<td>WE-0.65</td>
<td>+5</td>
<td></td>
</tr>
<tr>
<td>0310902*</td>
<td>Finger extension WE-0.59</td>
<td>WF-0.65</td>
<td>-131</td>
<td></td>
</tr>
<tr>
<td>9302601</td>
<td>Wrist flexion WF-0.43</td>
<td>WF-0.43</td>
<td>+104</td>
<td></td>
</tr>
</tbody>
</table>

Finger flexors were judged equivalent to wrist flexors because both acted across the wrist and because our surface electromyographic (EMG) recordings could not distinguish EMG activity arising from these two muscle groups. *, cells with significant correlation and a phase lead relative to EMG in the effector muscle (see text).

either antagonists or synergists. Because EMG activity in the effector muscle would produce the movement that caused a sensory response, thalamic activity might be expected to have a phase lag with respect to EMG activity in that muscle during dystonia (positive phase of the spike X EMG function). Results of this analysis are compiled in Table 5. Studies were limited to cells with RFs involving the wrist or elbow joint because EMG was studied only for muscles acting across these joints. A negative spike X EMG phase for the effector muscle was more common (73%, 8/11) than expected (P < 0.0005, Fisher exact) because thalamic activity would be expected to lag EMG in these muscles. This result suggested that sensory input to this cell might produce dystonia frequency activity that causes dystonia by transmission of that activity to the periphery.

This analysis of the spike X EMG function for the effector muscle also revealed that thalamic cells often were correlated with and phase-advanced relative to muscles other than the effector muscle. The proportion of cells with activity correlated with the effector muscle and with noneffector muscles is shown in Table 6. The results of this analysis demonstrate that thalamic cells commonly were correlated with and phase-advanced relative to EMG activity in noneffector muscles (86%, 18/21). Contrary to expectation, cells more often were correlated with the noneffector muscles than with the effector muscles (52%, 11/21, P < 0.02, Fisher exact; these 11 cells are listed in Table 5). Cells were as likely to be correlated with and phase advanced on noneffector muscles (52%, 11/21, P > 0.25, Fisher exact) as with effector muscles (38%, 8/21, these 8 cells are starred in Table 5). In dystonia patients, therefore, sensory input to thalamic cells was as likely to occur in advance of EMG activity in noneffector muscles as in the effector muscle (Butler et al. 1992a; Lenz et al. 1990).

FIG. 9. Muscle contractions evoked by thalamic stimulation in a patient with dystonia. A: lines under the lowest EMG recording indicate periods of microstimulation at 60 μA. This stimulation site (patient E) is indicated by the asterisk in Fig. 10, middle below the label for ventral intermediate (Vim). These stimulation-evoked contractions were similar to muscle contractions in dystonia because they involved simultaneous activation of multiple muscles (see Figs. 1 and 4). Muscle contraction was therefore identified as an increase in dystonia. B: stimulation-evoked contraction on a wider time scale.
Responses to microstimulation

Stimulation in presumed Vim often produced EMG activity in patients with dystonia, for example patient E (Fig. 9). At times when microstimulation was applied, there was a simultaneous increase in EMG activity in all muscles studied, similar to the simultaneous contraction of multiple muscles that is observed in dystonia (Fig. 4). In Fig. 9B the record of a burst of microstimulation is shown on an expanded time base; note the long latency of the evoked contraction.

Increases in dystonia were observed at 24 sites, whereas decreases in dystonia were found at only 2 sites. Increases in dystonia resulted from stimulation in 6 of 10 patients: 2 of 4 patients with primary dystonia and 4 of 6 with secondary dystonia. Of the six patients in whom stimulation increased dystonia, three had marked decrease in dystonia after lesioning, whereas lesioning had no effect on the other three patients. Stimulation had no effect on dystonia in three patients, of whom two had no benefit from the lesion, whereas the third patient had a good long-term result. A decrease in dystonia after lesioning was not significantly ($P > 0.05$, Fisher exact) more likely among patients in whom stimulation increased dystonia (3/6, 50%) than among those for whom stimulation decreased dystonia or had no effect (1/4, 25%).

Figure 10 shows the sites where stimulation influenced dystonia. In the 13.5-mm lateral plane, these sites were observed in presumed Vim, ventral Vc, and the adjacent white matter. In the 15.0-mm lateral plane, these sites were observed within presumed Vim, presumed Vop (one site), and ventral caudal parvocellular (Vcpc). In the 16.5-mm plane, one site was observed within, and one site above, presumed Vim. Most of the sites where stimulation influenced dystonia (15/24, 63%) were in presumed Vim. Simultaneous contraction of multiple muscles was evoked by stimulation more frequently in Vim (20%, 15/75) than in Vop (2%, 1/53; $P < 0.0001$, Fisher exact).

Thalamic lesions in patients with dystonia

Lesioning at a single site was sometimes associated with an immediate decrease in dystonia. The amount of spontaneous dystonia was reduced dramatically (Fig. 11) after the lesion at the estimated location shown in Fig. 12A (patient B, Table 1). The map of stimulation and recording sites (Fig. 12A) was aligned with the nuclear map by shifting the map of recording sites along the AC-PC line so that the most anterior cutaneous sensory cell was at the anterior border of Vc. Note that the estimated location (see METHODS) was centered in presumed Vop but involved part of presumed Vim. The lesion was located in a region containing deep sensory cells and/or cells with dystonia-related activity defined by SNR > 2 and coherence >0.42 (see METHODS).

A dramatic effect similar to that shown in Fig. 11 resulted from the lesion in patient H (Fig. 12B). This lesion was estimated to be located in presumed Vop and included cells showing activity correlated with dystonia. These results suggested that lesions decreasing dystonia involved presumed Vim or presumed Vop or both (see Somatic Sensory Activity).

DISCUSSION

The present results are the first report of thalamic neuronal activity in dystonia and suggest that different abnormalities occur in thalamic nuclei Vop and Vim. The activity of cells in presumed Vop, but not presumed Vim, is dominated by power at dystonia frequency (Table 3), and this activity often is correlated with and phase-advanced on EMG activity. The prevalence of dystonia frequency activity suggests that Vop may be involved in the mechanism of dystonia. Cells in presumed Vim in dystonia patients show changes in somatic sensory organization (Table 7). The thalamic representation of individual joints and the percentage of deep sensory cells in
presumed Vim was significantly greater in patients with dystonia than in controls. During dystonia, thalamic activity often was correlated with and phase-advanced on EMG activity in muscles other than the muscle producing the movement that caused cellular firing. Stimulation in Vim often increased simultaneous muscular contraction, similar to dystonia.

These results suggest that sensory input might drive the activity of cells in Vim to produce dystonia by transmission of that activity through altered somatic sensory maps to multiple muscles. This model could explain the cocontraction and overflow of muscular activation that are characteristic of dystonia (Hallett 1993; Rothwell et al. 1983).

Dystonia-related activity in the basal ganglia

The present study showed that power was concentrated at dystonia frequency for cells in presumed Vop (Table 3) and that lesions of this nucleus (Fig. 12B) can relieve dystonia. These results suggest that Vop plays a significant role in the mechanism of dystonia. Vop corresponds to monkey nucleus ventral lateral oral (VLo) (see references Hirai and Jones 1989a,b), the main termination of pallidal efferents (DeVito and Anderson 1982; Hendry et al. 1979; Jones 1985; Kim et al. 1976; Kuo and Carpenter 1973). VLo, in turn, projects predominantly to the motor cortex in the depths of the central sulcus (Holsapple et al. 1991) and to supplementary motor cortex (Holsapple et al. 1991; Jones 1985; Schell and Strick 1984). Neuronal activity at dystonia frequency dominates in presumed Vop and both correlates with and leads EMG activity. The high incidence of dystonia frequency activity in presumed Vop may reflect altered pallidal activity in dystonia patients, which is patterned in dystonia as grouped discharges at low frequency (Lenz et al. 1998b; Vitek et al. 1998). Because lesions of GPi (Vitek and Lenz 1998) and presumed Vop (see Figs. 11 and 12B) can relieve dystonia, these results suggest that patterned neuronal activity in Vop may be important in the mechanism of dystonia.

The mechanism of dystonia is usually explained in terms of the two broad categories of movement disorders: hypokinetic and hyperkinetic (Albin et al. 1989; DeLong 1990). Recent
studies in monkeys rendered parkinsonian after treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; “MPTP monkeys”) (Burns et al. 1983) suggest that thalamic spontaneous activity should be decreased in hypokinetic disorders like parkinsonism (Albin et al. 1989; DeLong 1990). Activity in VLo and VPLo of MPTP monkeys, corresponding to Vop and Vim, is characterized by decreased firing rates (Vitek et al. 1994b) and increased responsiveness to somatic stimuli (Vitek et al. 1990). Consistent with dystonia’s being a hypokinetic disorder, like Parkinson’s disease, the present study documents decreased thalamic firing rates (see Table 2) and increased thalamic responses to somatic sensory stimuli (Fig. 7). If dystonia is a hypokinetic disorder, then thalamic lesions may be effective (Andrew et al. 1983; Cardoso et al. 1995; Cooper 1976; Gros et al. 1976; Laitinen 1970; Tasker et al. 1988) by interrupting abnormally patterned thalamic activity during dystonia (see Table 7). On the other hand, dystonia has been called a hyperkinetic disorder based on studies of MPTP monkeys rendered dystonic after treatment with levodopa (Mitchell et al.

Dystonia may fit neither the hypokinetic nor the hyperkinetic model.

It also has been suggested that dystonia is characterized by disinhibition of the indirect pathway from striatum to pallidum (Perlmutter et al. 1997), which may lead to loss of surround inhibition in the pallidum and motor system (Mink 1996). Surround inhibition is proposed to allow isolated movements to occur by inhibiting unwanted associated movements (Mink 1996). Loss of surround inhibition might explain the mismatch between effector muscles and muscles with EMG activity correlated with neuronal activity (Table 6). This mismatch is consistent with the cocontraction and overflow of muscular activation that are characteristic of dystonia (Hallett 1993; Rothwell et al. 1983).

Methodologic considerations

Because cellular location cannot be determined precisely in human studies, we estimated nuclear location from both radiological and physiological data. In previous human studies, the anterior border of Vc was estimated from the position of the most anterior cell in the region where the majority of cells had either deep or cutaneous RFs (Lenz et al. 1990, 1994c). In the present study, the region where most cells have a deep RF clearly extended far anterior to the anterodorsal shell of Vc (Figs. 5 and 7) (see also Figs. 1 and 2 in Hirai and Jones 1989b). For this reason, the anterior border of the region where cells had cutaneous RFs was assumed to be the anterior border of Vc, as a first approximation of nuclear location.

The location of deep sensory cells in presumed Vim of the present study (Fig. 5), corresponding to monkey VPLo (Hirai and Jones 1989a), may raise the concern that presumed Vim is actually an enlarged anterodorsal shell of Vc (Friedman and Jones 1981; Jones et al. 1982). However, recent studies of awake monkeys establish the presence of large numbers of cells with deep somatic sensory RFs in VPLo and VLo (Anderson and Turner 1991; Butler et al. 1992; Vitek et al. 1994a), corresponding to human Vim and Vop (Hirai and Jones 1989a). These studies suggest that the region containing cells with deep RFs includes the anterodorsal shell of Vc as well as presumed Vim and presumed Vop.

Another concern of this study was the effect of arm position (pointing vs. at rest) on thalamic and EMG activity. To explore

TABLE 7. Summary of thalamic cellular activity among dystonia patients

<table>
<thead>
<tr>
<th></th>
<th>Presumed Vop</th>
<th>Presumed Vim</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia frequency peak, %</td>
<td>81</td>
<td>32</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Dystonia frequency peak correlated with dystonia, %</td>
<td>28–46</td>
<td>13–23</td>
<td>NS</td>
</tr>
<tr>
<td>Dystonia frequency peak leading dystonia, %</td>
<td>50–83</td>
<td>66–100</td>
<td>NS</td>
</tr>
<tr>
<td>Number of deep sensory cells in dystonia of control patients, %</td>
<td>11 of 4 (NS)</td>
<td>28 of 11 (&lt;$P &lt; 0.01$)</td>
<td>—</td>
</tr>
<tr>
<td>Thalamic stimulation evoked dystonia, %</td>
<td>2</td>
<td>20</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Thalamic lesions can increase dystonia</td>
<td>yes</td>
<td>yes</td>
<td>—</td>
</tr>
</tbody>
</table>

Significance are in parentheses in fourth row.

FIG. 12. Locations of single thalamic lesions producing a decrease in dystonia. Locations of lesions relative to stimulation and recording sites are shown. Recording sites for cutaneous and deep sensory cells and for cells with dystonia-related activity. A: 1st lesion in patient B. B: 1st lesion in patient H. Images planes of trajectories are indicated in mm lateral to the midline. The 13.5 and 15 mm lateral sagittal atlas maps were used in A and B, respectively (Schaltenbrand and Bailey 1959). Scale as marked.
this question, we examined the frequency of peak EMG activity, mean ISI, peak spike activity, frequency of peak spike activity, and spike X EMG coherence as a function of position. Differences between the arm pointing and at rest were not significant for any of these variables. This finding suggests that comparisons with control patients were valid regardless of arm position.

The control group for thalamic activity (patients with pain) had significant neurological pathology so that spontaneous activity in Vim and Vop might have been abnormal. To address this concern, we compared the mean ISI duration to that in the corresponding nuclei of normal waking monkeys. Average ISIs in Vim of controls with pain (0.076 s) were similar to those recorded in the corresponding monkey nucleus (VPLo) of African Green monkeys (0.046 s) (Vitek et al. 1994a) and cynomolgous monkeys during the hold period before a cue to movement (0.050 s) (Anderson and Turner 1991). Average ISIs in Vop of controls with pain (0.059 s) were similar to those recorded in the corresponding nucleus (VLo) of African Green monkeys (0.053 s) and cynomolgous monkeys (0.075 s). These results suggested that thalamic firing rates in control patients with pain were similar to that recorded in other primates and higher than those recorded in patients with dystonia (Table 2).

Differences among dystonia patients might constitute a flaw in this study. However, such differences were not significant in terms of concentration of EMG activity in the lowest frequency band, probability of cocontraction, mean thalamic neuronal ISI, or concentration of spike activity in the lowest frequency range. Stimulation evoked simultaneous contractions of many muscles in similar proportions of patients with primary or secondary dystonia. Thalamotomy achieved good results in two of four patients with primary and two of six patients with secondary dystonias (Table 1). Thus studies of EMG activity, thalamic activity, responses to thalamic stimulation, and responses to lesions suggest that upper extremity dystonia in these patients was similar, regardless of etiology.

Somatic sensory activity

RESPONSES OF CELLS IN VIM AND VOP. The number of deep sensory cells in presumed Vim was higher in patients with dystonia than in the controls with pain and tremor (Fig. 7 and Table 4). Although we controlled for methodologic differences by correcting for nuclear location, we cannot exclude differences in the explorations of these patients as an explanation of the results. The number of cells in presumed Vim and presumed Vop responding to somatic sensory inputs in both the dystonia and control groups is similar to the results of early studies (Horne and Porter 1980; MacPherson et al. 1980; Strick 1976) but not recent studies in alert monkeys (Anderson and Turner 1991; Butler et al. 1992; Vitek et al. 1994a). These latter studies in monkeys reveal responses to passive movements for 71–90% of cells in VPLo (Anderson and Turner 1991; Butler et al. 1992; Vitek et al. 1994b), the nucleus corresponding to human Vim (Hirai and Jones 1989a). Responses to passive movement are found in 40–60% of cells in monkey VLO (Anderson and Turner 1991; Butler et al. 1992; Vitek et al. 1994a), which corresponds to human Vop (Hirai and Jones 1989a).

Several explanations may account for the discrepancy between the number of deep sensory cells in the present study and those reported in recent monkey studies. Some of the monkey responses may be related to “slight muscle contractions that the monkeys made in response to examinations” (Anderson and Turner 1991); this effect might lead to an overestimate of neurons responsive to somatic sensory stimulation. Also time constraints of the operative procedure may have resulted in somatic sensory examinations that were less complete in humans than in monkeys. Finally, human cellular locations are inferred from stereotactic coordinates corrected to the anterior border of the core of Vc, an inference that is less reliable than the histological reconstructions used in monkey studies. If cells in adjacent nuclei are localized incorrectly in presumed Vim or presumed Vop, then the estimate of deep sensory cells in these latter nuclei may be artificially low. In this study, however, because the same techniques were used in both the control and dystonia groups, we considered comparison of the two patient groups to be valid.

The presence of dystonia might alter sensory examinations in the present study. When a high level of cocontraction is present in a limb, as in dystonia (Fig. 4), passive movement of one joint may be mechanically transmitted to another joint in the limb. Thus movement of several joints might appear to evoke responses in a cell that is, in fact, only activated by movement of a single joint. Among dystonia patients this effect could explain the increased numbers of cells with activity driven by movement of more than one joint. Still, cocontraction would not be expected to cause cells unresponsive to sensory stimuli to be misidentified as sensory cells. Therefore the level of cocontraction cannot account for the increase in the number of deep sensory cells. Because cocontraction could increase the size of the representation of individual joints in patients with dystonia, our analysis included only cells activated by movement of a single joint.

ORIGIN OF SENSORY INPUTS TO VIM AND VOP. The origin of sensory inputs to the cerebellar and pallidal relay nuclei is uncertain. Studies in monkeys show that cells in VPLo projecting to the motor cortex (Horne and Tracey 1979; Lemon and van der Burg 1979; Wiesendanger and Miles 1982) respond at short latency to peripheral stimulation (Asanuma et al. 1980; Horne and Tracey 1979; Vitek et al. 1994a). These somatic sensory responses may involve transmission of somatic sensory signals through the dorsal column or spinthalamic tracts (Berkley 1983; Greenan and Strick 1986; Jones 1985; Lenz et al. 1990; Tracey et al. 1980; Wiesendanger and Miles 1982). However, the spinothalamic tract may not terminate in the part of VPLo that projects to motor cortex (Greenan and Strick 1986), and dorsal column nuclei may (Berkley 1983) or may not (Tracey et al. 1980) project to VPLo in monkeys. Finally, sensory inputs to the thalamic cerebellar relay nucleus might involve transmission of sensory input through cortex either directly through corticothalamic projections (Berkley 1983; Greenan and Strick 1986; Jones 1985; Lenz et al. 1990; Tracey et al. 1980; Wiesendanger and Miles 1982) or via cerebellum to thalamus (Brooks and Thach 1981).

Somatic sensory responses of cells in the pallidal relay nucleus, monkey VLo, might be explained by input from sensory cortex and area 3A (Flaherty and Graybiel 1993; Fotuhi et al. 1988) to regions of striatum that project to VLo via the pallidum (Alexander et al. 1986; Hedreen et al. 1988).
Sensory stimulation evokes responses in a proportion of pallidal cells (DeLong and Georgeopoulos 1981) and cells in VLo of normal monkeys (Anderson and Turner 1991; Butler et al. 1992b; Vitek et al. 1990, 1994a). In the pallidum, the average latency of responses to sensory stimulation is much longer than that in the motor cortex (DeLong et al. 1985). This longer time is consistent with the significant delay in responses to torque motor-evoked elbow movements for cells located in VLo (mean 47 ms) as compared with that for cells in the anterodorsal shell of VPLc (22 ms) (Vitek et al. 1994a). Sensory responses in pallidal relay nuclei also might be explained by corticothalamic connections (Jones 1985). In summary, a wide range of possibilities might explain the sensory responses found in the present study.

**REFLEX FUNCTION IN PATIENTS WITH DYSTONIA.** There is considerable evidence of abnormal reflex function in dystonia. For example, vibration of the palm is reported to evoke dystonic postures in patients with writer’s cramp, a form of focal dystonia, but not in controls (Kaji et al. 1995). Writer’s cramp is reduced markedly by intramuscular injection of local anesthetic to block tendon reflexes but not muscle contractions evoked by peripheral nerve stimulation. As another example, contraction of muscles shortened by passive joint rotation, the Westphal phenomenon, is elicited “with ease” in cases of dystonia (Rothwell et al. 1983; Yanagisawa and Goto 1971). This phenomenon may be related to the loss, in dystonia, of reciprocal inhibition by which 1A afferents from forearm extensors inhibit forearm flexors (Deuschl et al. 1992; Marsden and Rothwell 1987; Pannizza et al. 1990). This effect could involve CNS processing of afferent signals and may explain the phenomenon of antagonist co-contraction (Cohen and Hallett 1988; Yanagisawa and Goto 1971).

These abnormal reflex effects could be mediated by reflex arcs traversing the thalamus. Long-latency (M2) reflex responses to torque motor-imposed wrist joint displacement show normal amplitude (Rothwell et al. 1983; Tatton et al. 1984) but abnormally prolonged duration in dystonia (Marsden and Rothwell 1987; Tatton et al. 1984). Long-latency reflex components might be generated (Cheney and Fetz 1984; Desmedt 1978; Ghez and Shinoda 1978; Lenz et al. 1983; Marsden et al. 1973; Matthews 1984) by transmission of muscle afferent activity through reflex arcs that traverse thalamus and cortex before being transmitted back to the periphery. According to this hypothesis, the abnormal duration of long latency reflexes in patients with dystonia suggests an abnormal processing of afferent activity in the CNS.

**Thalamic microstimulation and lesions in patients with dystonia**

The effects of thalamic stimulation and lesions on dystonia suggest that the cellular abnormalities observed in presumed Vim and presumed Vop are involved in the mechanism of dystonia. Microstimulation in presumed Vim evokes EMG activity in dystonia patients, a result that might be attributed to stimulation of the adjacent internal capsule (Schaltenbrand and Bailey 1959) except that stimulation in Vim of patients with chronic pain (Lenz et al. 1998a) does not produce motor effects. The sites where stimulation evokes EMG activity in patients with dystonia are found largely in presumed Vim. Alterations in dystonia by microstimulation in Vim may be related to the muscle twitches evoked by microstimulation in VPLo of monkeys (Buford et al. 1996; Strick 1976; Vitek et al. 1996), which corresponds to human Vim (Hirai and Jones 1989a). Recent studies report that muscle twitches occur in response to stimulation in the cerebellar relay nuclei (including VPLo) but not the pallidal relay nuclei of thalamus (Buford et al. 1996; Vitek et al. 1996). One of these studies reports physiological confirmation of the relay nuclei by thalamic responses to stimulation of the cerebellar nuclei or GPi (Buford et al. 1996). In patients with dystonia, the stimulation-evoked activity shows simultaneous contraction of multiple muscle groups (Fig. 9) characteristic of dystonic movements (Figs. 1 and 4). The present results thus suggest that activation of Vim by microstimulation can drive dystonia.

The effect of lesions in Vim and Vop on dystonia is well described (Cardoso et al. 1995; Gros et al. 1976; Narabayashi 1982; Tasker et al. 1988). In all reports, dystonia is decreased in a proportion of patients, although the improvement may be delayed (Cardoso et al. 1995) and the dystonia sometimes returns with time (Cardoso et al. 1995; Gros et al. 1976; Tasker et al. 1988). The present results indicate that a small lesion (>30 mm³) involving presumed Vop and presumed Vim can produce an immediate decrease in dystonia (Figs. 11 and 12). Therefore stimulation in Vim can drive movements with co-contraction-like dystonia, and lesions in Vim and Vop can decrease dystonia. These observations strongly suggest that abnormal neuronal activity in these nuclei is involved in the generation of dystonia.

**Somatic sensory activity: role of thalamic nuclei in the mechanism of dystonia**

The present results reveal an increased representation of deep structures in Vim in the affected extremity in dystonia patients. Lengths of electrode trajectories along which cells had RFs for a single joint (Lenz et al. 1994b), either wrist or elbow, were longer in patients with dystonia than in control patients. Because all of the patients studied had upper extremity dystonia (Table 1), this result suggests an increased representation of parts of the body with dystonia. Similar increases in the size of representations of joints are found in monkey motor cortex after repetitive movements involving those same joints (Nudo et al. 1996). Sensorimotor cortical areas in which magnetic stimulation evokes forearm movement are increased in patients with dystonia (M. Hallett, personal communication). In sensory cortex, increases in representations of cutaneous structures in the hand, as well as increases in receptive field sizes, are found after training to a repetitive gripping task that produces abnormalities of posture and movement similar to dystonia (Byl et al. 1996). The present study showed significant increases both in the representation of wrist and elbow (Fig. 8) and in RF size, as indicated by increases in multijoint RFs (Fig. 5).

Changes in sensory organization of Vim may contribute to the development of dystonia or may be an epiphenomenon—the passive result of dystonic movements. The correlation and phase lead of neuronal activity in presumed Vim with dystonic movements, in addition to the effects of thalamic microstimulation and lesions (see previous section), suggest that activity in Vim drives dystonia. In total, the present data argue forcefully that sensory reorganization of Vim contributes to the development of dystonia.
The present data and previous studies suggest the mechanism by which reorganization may contribute to dystonia. Specifically, the mismatch between effector muscles and muscles correlated with dystonia (see Table 6) is reminiscent of findings in patients with spinal transection (Lenz et al. 1994b) or amputation (Lenz et al. 1998c). In both of these groups of patients, the reorganization of the thalamic map of RFs leads to a mismatch between RFs (input) and the part of the body where thalamic microstimulation evokes sensation (projected field, output) (Lenz et al. 1998c). These patients have somatotopic reorganization of RF (input) maps but have less complete reorganization of the projected field map (output) (Lenz et al. 1998c). In dystonia, there may be a similar failure of the muscles correlated with thalamic spike activity to reflect the changes in the RF produced by shifts in the sensory map.

This mismatch between muscles in the RF and those correlated with dystonia may cause somatic sensory input to be transmitted to multiple muscles other than the effector muscle (Table 6). This mismatch might produce the cocontraction and the overflow of muscle activation that are characteristic of dystonia (Hallett 1993; Rothwell et al. 1983). A model of such a condition may be the stump jerks that occur in some patients with amputation (Marion et al. 1989). Stump jerks have features of dystonia (W. Olson, personal communication) and affect a population with demonstrated reorganization of thalamic maps (Lenz et al. 1998c). This type of reorganization also may produce focal dystonias that occur in patients whose occupations (e.g., musicians) include repetitive motor tasks performed under high cognitive drive (Byl et al. 1996; Hochberg et al. 1983).

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REFERENCES


