THE COEXISTENCE OF BRADYKINESIA AND CHOREA IN HUNTINGTON’S DISEASE AND ITS IMPLICATIONS FOR THEORIES OF BASAL GANGLIA CONTROL OF MOVEMENT

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SUMMARY

Investigation of motor function in a group of 17 patients with Huntington’s disease reveals that, in addition to the chorea that many patients exhibit, defects in voluntary motor performance also are evident. Fast simple wrist flexion movements to 15° or 60° were slower, and individual movements showed greater variability than seen in normal subjects. This bradykinesia was most pronounced in those patients who were akinetic and rigid, but also was seen in those with chorea alone; bradykinesia was independent of the drug treatment that the patients were receiving (and was therefore not due to drug-induced parkinsonism). The electromyographic activity of the agonist muscles during such simple but slow movement differed from that seen in Parkinson’s disease. The performance of complex movements revealed further deficits. Some patients were unable to combine two movements in a simultaneous or sequential movement task of squeezing the hand and flexing the elbow. Those who could perform these complex movements exhibited slowing of the velocity of the movement and prolongation of the interval between movements. These abnormalities were present in patients with chorea who were not taking neuroleptic drugs. It is argued that they represent an abnormality of motor programming of complex movements, over and above the defect in executing simple movements. The long latency stretch reflexes in wrist flexor muscles and flexor pollicis longus were reduced or absent, but this did not correlate with changes in motor performance, or with the reduced size of the early components of cortical sensory evoked potentials. Bradykinesia is thus shown to be an integral component of the motor disorder of Huntington’s disease, in addition to the chorea. The coexistence of bradykinesia and chorea in this illness is compatible with current theories of the role of the basal ganglia in the control of movement.

INTRODUCTION

Although the most conspicuous abnormality of movement in Huntington’s disease is chorea, involuntary movements may not be the sole, or even the major source of motor disability in this condition. Several authors have drawn attention to the...
fact that pharmacological suppression of chorea may not lead to improvement of motor function (Shoulson, 1981; Girotti et al., 1984; Quinn and Marsden, 1984; Koller and Trimble, 1985). An underlying deficit reminiscent of the akinesia/bradykinesia of Parkinson’s disease remains or even deteriorates with treatment of the chorea. Indeed, some patients with Huntington’s disease may present with an akinetic-rigid syndrome (the’Westphal’ variant) without typical chorea, and it is well known that with the passage of time and progression of the disease, chorea may subside and an akinetic-rigid and often dystonic syndrome emerges (Hamilton, 1907–8; Denny-Brown, 1960; Bittenbender and Quadfasel, 1962; Hayden, 1981).

These clinical observations hint at the concept that akinesia/bradykinesia may be a fundamental motor abnormality in Huntington’s disease in addition to the characteristic chorea. Such a conclusion would be in keeping with contemporary concepts of the motor functions of the basal ganglia, which conceive of these structures as necessary for the initiation and execution of movements. However, there have been relatively few studies into the motor pathophysiology of Huntington’s disease.

Studies of gait (Koller and Trimble, 1985) have disclosed abnormalities resembling those in Parkinson’s disease; patients had difficulties initiating gait and in turning, and there was an increased step cycle time and slow leg swing. Hefter et al. (1987) have reported slowing of finger movements. Moreover, there may be striking slowing of voluntary saccadic eye movements in some patients with Huntington’s disease (Starr, 1967; Leigh et al., 1983) in contrast to the limb chorea.

Despite clinically normal sensory function, cortical somatosensory evoked potentials (SEPs) to peripheral nerve stimulation may be small or absent (Noth et al., 1984, Bollen et al., 1985), while long-latency stretch reflexes are often absent (Noth et al., 1985). In contrast to these afferent abnormalities, the corticomotoneuron connections as tested by electrical stimulation of the motor cortex, conduct normally (Thompson et al., 1986). The relationship of the disturbances of the central processing of afferent information to the disorder of movement remains unclear.

In the present paper we have examined the voluntary control of simple movements and complex simultaneous and sequential movements of the arm and hand in patients with Huntington’s disease of varying severity. The clinical signs, voluntary movements, SEPs and stretch reflexes in individual patients were assessed to see if any correlation existed between them. The results will be discussed in the light of the known pathophysiological changes that occur in Parkinson’s disease, a disorder of the basal ganglia which presents a clinical syndrome of akinesia/bradykinesia, in contrast to the hyperkinesia of Huntington’s disease. Part of this work has been published in abstract form (Berardelli et al., 1985; Thompson et al., 1985).
PATIENTS AND METHODS

Patients

The clinical features of the 17 patients with Huntington's disease in this study are summarized in Table 1. They comprised 9 males and 8 females aged between 36 and 67 yrs (mean age 48 yrs) with a disease duration of between 4 and 20 yrs (mean 10 yrs). The diagnosis of Huntington's disease was established on the basis of the clinical features and a family history of the disease in all cases. The patients have been ranked in the table on clinical grounds, according to the severity of their chorea.

Table 1. Summary of clinical features, drug therapy, long-latency stretch reflexes (SR) and cortical sensory evoked potentials (SEPs) in 17 patients with Huntington's disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Disease duration (yrs)</th>
<th>Drugs</th>
<th>FF</th>
<th>FPL</th>
<th>SEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akinetic-rigid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>F</td>
<td>20</td>
<td>Pimozide</td>
<td>+</td>
<td>NP</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>F</td>
<td>10</td>
<td>Tetrabenazine, pimozide, thiopropazate</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>M</td>
<td>15</td>
<td>Pimozide</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>7</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild to moderate chorea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>6</td>
<td>Baclofen</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>M</td>
<td>8</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>M</td>
<td>15</td>
<td>Baclofen</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>M</td>
<td>10</td>
<td>Sulpiride</td>
<td>+</td>
<td>+</td>
<td>NE</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>F</td>
<td>4</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>67</td>
<td>M</td>
<td>10</td>
<td>Baclofen</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Severe chorea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>37</td>
<td>M</td>
<td>9</td>
<td>Tetrabenazine, pimozide</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>F</td>
<td>15</td>
<td>Pimozide</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>40</td>
<td>F</td>
<td>5</td>
<td>Pimozide</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>46</td>
<td>F</td>
<td>14</td>
<td>Tetrabenazine, pimozide</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>58</td>
<td>F</td>
<td>15</td>
<td>Tetrabenazine, tiapride</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>M</td>
<td>10</td>
<td>Tetrabenazine</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>36</td>
<td>M</td>
<td>5</td>
<td>Tetrabenazine</td>
<td>+</td>
<td>NP</td>
<td>-</td>
</tr>
</tbody>
</table>

FF = forearm flexors; FPL = flexor pollicis longus. + = present; - = absent; NP = not possible; NE = not examined.

Four patients were akinetic (Cases 1–4), 1 (Case 1) profoundly so, to the extent that she was capable of very little voluntary movement, and unable to perform the simple test of wrist flexion. The other patients in this group were akinetic with varying degrees of rigidity and exhibited only occasional chorea of the limbs, face and trunk. Three of these 4 akinetic patients were taking neuroleptic drugs (pimozide, tetrabenazine and thiopropazate), but the fourth was on no treatment.

Six patients (Cases 5–10) had mild chorea which, in general, did not interfere with their ability to perform simple tasks; all managed daily activities at home and were independent with some assistance. One was taking a neuroleptic (sulpiride), 3 were on baclofen and 2 were untreated.

Seven patients (Cases 11–17) had severe chorea, and were significantly disabled. They experienced considerable difficulty in performing most voluntary movements, but were able to cooperate with the test procedures. All these patients were taking neuroleptic drugs (pimozide, tetrabenazine and tiapride).

Nine of the 11 patients with severe chorea or akinesia required nursing care for daily activities.

For comparison, the simple wrist movements of a group of 8 normal subjects aged 30 to 63 yrs (mean 47 yrs), the complex movements of 9 normal subjects aged 31 to 67 yrs (mean 47 yrs), the stretch reflexes from 12 normal subjects aged 30 to 69 yrs (mean 44 yrs) and the somatosensory evoked potentials from 11 normal subjects aged 28 to 65 yrs (mean 40 yrs) were studied.
Methods

To analyse the distribution, pattern and duration of choreic movements, surface electromyographic (EMG) activity was recorded from different limb muscles including the thenar, flexor and extensor muscles in the forearm, biceps, triceps, tibialis anterior and triceps surae muscles. Recordings were obtained when the subjects were at rest, and while they were performing a motor task or maintaining a posture.

Surface EMG recordings were made using bipolar silver/silver chloride surface electrodes placed over the bellies of the muscles. The signals were preamplified (Devices 3160 band-width from 80 Hz–2.5 kHz, 3 dB points) then amplified (Devices 3120 amplifier) and recorded by a PDP 12 computer using a sampling rate of 500 Hz per channel.

Simple movements

Rapid wrist movements were studied while the patients were seated comfortably in a chair with their forearm held semipronated and strapped to a platform at their side, with the fingers encased in a rigid splint. The mechanical consequences of the movement were monitored by a potentiometer, mounted coaxially with the wrist joint, which signalled the angular position of the wrist. The angular velocity of wrist movement was obtained by analogue differentiation of the position signal. Rectified EMG activity was recorded from the extensor and flexor muscles in the forearm.

The subjects were asked to make rapid wrist flexion movements of 15° and 60° in their own time starting from an initial joint angle of 30° wrist extension. Wrist and target positions were displayed on an oscilloscope in front of the patients who were instructed to align the two marker spots as rapidly as possible. Accuracy was not stressed.

Because of the variability of the patients' movements from trial to trial, and the difficulty in separating voluntary activity from chorea, 20–30 single movements to 15° and 60° targets were recorded from each patient. Out of these, 10 or so trials from each patient were selected in which the onset of the movement was clear (see fig. 3 for examples) and the onset and duration of agonist EMG activity was easily identified. In 3 patients this was not possible and the movements were not measured. These selected trials were then used for comparison with results from control subjects. The amplitudes and velocities of the movements were measured, and the duration of the EMG bursts in the agonist muscle was measured from the rectified EMG records by visual inspection.

The total group of patients was compared with the normal age-matched control group of subjects. In addition, the individual subgroups of patients identified on clinical grounds according to the severity of chorea (akinetik, mild-moderate and severe) were compared with each other and with the normal subjects. A separate grouping of the patients with chorea also was undertaken with respect to the medications they were receiving. Those patients with chorea who were receiving neuroleptic drugs, and who were able to perform the simple movements (n = 5), were compared with those who were not receiving such medications (n = 5). Comparison of groups using data combined from both 15° and 60° movements was made using a two-way analysis of variance (ANOVA) for repeated measures. The coefficient of variation for the position and velocity measurements (1 SD/mean) for patients compared with controls was made using Student’s t test.

Complex movements

In selected patients (Cases 4, 5, 7, 9, 10, 13) a more complicated series of movements was examined. These patients exhibited varying degrees of severity of chorea. One was relatively akinetic; 4 others had mild to moderate chorea and 1 had severe chorea. Two were not taking any drugs; 3 were taking baclofen only and 1 took pimozide.

The experimental procedure for examination of simultaneous and sequential movements has been described in detail previously (Benecke et al., 1986, 1987). Briefly, patients were seated with their right arm abducted at 90° at the shoulder. The forearm rested on a manipulandum coaxial with the elbow joint. Angular position of the elbow was monitored by a potentiometer attached to the pivot
of the manipulandum. A strain gauge was attached to a U-shaped metal bar at the end of the manipulandum and was grasped between the thumb and fingers. The different movements studied were as follows: single flexions of the elbow through an angle of 15° from a starting angle of 135° ('flex'); single squeezes of the strain gauge to exert a force of 30 N ('squeeze'); both these tasks at the same time ('squeeze and flex'); and both tasks in sequence ('squeeze then flex'). The patients were instructed to perform each movement as rapidly as possible. For the sequential movements the patients were instructed to perform the squeeze movement and immediately on completion of this, flex their elbow.

The elbow position and force of grip were displayed as two vertical bars on an oscilloscope screen in front of the patient. After a series of practice trials 10 single trials of each task were collected. Trials were excluded from analysis if they were not simultaneous or sequential, or if the movements were performed in the wrong order. The movements were carefully monitored by an observer and those which appeared to have been contaminated or interrupted by chorea were excluded from the analysis.

EMG activity was monitored in the biceps and opponens pollicis muscles in the manner described above. The velocity of the elbow movement (electronically derived from the position signal), the force of hand squeeze, and rectified EMG were recorded as above. For the sequential movement tasks, the interval between the onset of the first and second movement (the interonset latency, IOL) was also measured. This time includes the duration of the first movement. In order to exclude the contribution of prolongation of the first movement time to the IOL, the movement time of the first movement was subtracted from the IOL, to give an indication of the pause between the two movements.

For the complex simultaneous and sequential movements, the movement times for the elbow flexion movement were compared by Student’s t test with those from the group of normal control subjects when the movements was performed alone and as part of a complex movement.

Stretch reflexes

The stretch reflexes in the forearm flexor muscles were studied using the same device described for the ballistic wrist movements, with the forearm semipronated and strapped to a platform. The subjects were requested to maintain a constant position of their wrist (160° flexion) against a background torque (0.25 Nm) produced by a torque motor (Printed Motor G12M). Muscle stretches were given every 5 s by a sudden increase in motor torque to 1 Nm and 1.5 Nm. The duration of the imposed displacement was 200 ms.

The general method for analysing the stretch reflexes in the flexor pollicis longus has been described in detail previously (Marsden et al., 1976). The proximal phalanx of the thumb was clamped, allowing movements only of the interphalangeal joint, with the pad of the thumb resting on a lever attached to the spindle of a torque motor (Printed Motor G9M4H). Thumb angular position was given by a potentiometer mounted on the motor shaft. EMG activity was recorded by surface electrodes from the flexor pollicis longus muscle. The subjects were requested to maintain a constant thumb position against a background torque 0.07 Nm. Muscle stretches were produced by sudden increase in motor torque to 0.14 and to 0.21 Nm. The duration of the stretches was 200 ms and stretches were applied every 5 s.

For both the forearm and thumb stretches, the average of 32 trials was recorded, and the latency and the duration of both the short and long latency EMG reflexes were measured. The size of the reflex was obtained by integrating the rectified EMG activity and expressing it as the percentage increase in activity over baseline levels obtained from control trials in which no stretch was applied. The stretch reflexes were compared with those from a control group of 12 subjects by Student’s t test.

Cortical somatosensory evoked potentials

SEPs were recorded from electrodes placed over the contralateral scalp, 2 cm posterior to C3 and C4 (International 10/20 system) with reference to Fz, after electrical stimulation of the median nerve.
at the wrist, just above motor threshold. Recordings were also made from electrodes placed over Erb's point and the neck at the level of C4. In each patient, two series of 1000 responses were averaged, with filters 3 dB down at 80 and 2.5 kHz. The amplitude of the N1 (N20) component of the primary cortical response was measured in two ways: from baseline to peak, and from the N1 peak to the following positive peak (referred to here as P1). The amplitude of the following negative wave was also measured (P1–N2).

The latency values were compared with the normal group by Student's t test. The amplitude measurements were complicated by the fact that in some patients there was no detectable primary component of the SEP. When comparisons were made including these zero values, a Mann-Whitney U test was used; otherwise the data were transformed logarithmically to obtain a normal distribution, and compared using Student's t test (Lüders, 1970).

Spearman rank correlation coefficients between the sizes of the individual components of the cortical evoked potential and the size of the stretch reflexes also were calculated. Finally, the velocity of 60° wrist movements was chosen as a measure of motor performance to see if any correlation existed between the sensory evoked potentials, stretch reflexes and movement performance. Spearman rank correlation coefficients were calculated.

**RESULTS**

*Simple voluntary movements*

Normal subjects performed rapid voluntary wrist flexion movements with a biphasic or triphasic pattern of EMG activity in the agonist and antagonist muscles. Movements of larger amplitude were accomplished with a greater angular velocity. These were produced by an agonist burst that was larger in size and slightly longer in duration than that for smaller movements (see Hallett and Marsden, 1979; Berardelli *et al.*, 1984).

Thirteen of the patients studied were able to perform the task satisfactorily so as to achieve movements of 15° or 60°; in all these patients it was possible to measure the EMG activity in the agonist muscle and its mechanical consequences,
defined by the movement amplitudes and the angular wrist velocity. In 4 patients it was not possible to make such measurements because of considerable irregularity and variability of the movement trajectory, with poor definition of the onset and duration of the agonist EMG burst.

The mean angular velocities in the 13 patients for both large and small amplitude wrist movements were slower than normal (ANOVA at 15° and 60° F (1, 19) = 25.87, P<0.001) (fig. 1). In addition, this analysis revealed a small but significant interaction between angular wrist velocity and wrist position (F (1, 19) = 8.08, P<0.05). This suggested that the relationship between velocity and intended wrist position

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)

**Fig. 2.** A, mean (± 1 SE) angular velocity of voluntary wrist flexion movements of amplitudes 15° and 60° in 8 normal subjects (open bars) and 13 patients with Huntington’s disease (hatched bars). The latter have been separated into subgroups according to their clinical signs; the wrist movements in all 3 groups were slower than normal and those in the akinetic-rigid group were slower than in the mild group (ANOVA, P<0.01). B, speed of wrist movements in the group of patients with chorea (n= 10) who were receiving neuroleptic drugs (n = 5). This was not significantly different (P>0.05) from those who were untreated or taking baclofen (n = 5); both these groups also were slower than normal (ANOVA, P<0.01). C, D, variability in angular velocity, final position (amplitude of movement) and duration of the first agonist EMG burst (Ag1) for wrist flexion movements of 15° (c) and 60° (d) for normal subjects (n = 8) (open bars) and patients with Huntington’s disease (n = 13) (hatched bars), expressed as the mean (± 1SD) coefficient of variation (SD/mean). The coefficient of variation in the patients for each measurement of movement performance was significantly different from normal subjects, indicating a greater variability (Student’s t test: **P<0.01; ***P<0.001).
in the patients differed from that in normal subjects. The angular velocities for both amplitudes of movement were slower than normal when compared by Student's t test (15°, \( P < 0.05 \); 60°, \( P < 0.001 \)). When the individual groups of patients were considered, movement speed was slower than normal in each category (fig. 2A); those patients who were rigid and relatively akinetic were slower in comparison with those who had mild chorea (ANOVA at 15° and 60°, \( F (1, 7) = 13.95, P < 0.01 \)) (fig. 2A). Among the patients with chorea (mild or severe) (n = 10), the speed of movements of those receiving neuroleptic medications (n = 5) was not significantly

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**Fig. 3.** Wrist position, angular velocity, and rectified EMG traces from forearm flexor (FF) and extensor muscles (FE) during 4 separate voluntary wrist movements attempting to reach 60° in a 46-yr-old patient with a 14 yr history of Huntington's disease (Case 14). The patient had severe chorea and was taking tetrabenazine and pimozide. The 4 movements illustrate the variable movement trajectory and patterns of agonist and antagonist muscle activation during consecutive movements. Only the movements in the upper right and lower left panels would have been measured from these trials, as the wrist position in the upper left panel was displaced by chorea before the onset of wrist flexion; in the lower right panel, the onset of the movement is not clear.
different to those who were receiving baclofen or no drugs (n = 5) (ANOVA at 15°
and 60°, F (1, 8) = 2.57, P > 0.05) (fig. 2B).

The mean data of fig. 1 obscure the variability seen from trial to trial in each
subject. In fact, the variability in peak velocity and end position was far greater in
the patients than in normal subjects (fig. 2C, D).

A biphasic pattern of EMG activity in agonist and antagonist muscles which is
typical of rapid wrist movements in normal subjects, was seen only in the group
of patients with mild chorea. Those patients with severe chorea and those who
were akinetic exhibited a variety of combinations of EMG activity, in which the
agonist burst varied from trial to trial (fig. 3). This degree of variability was
greater than that seen in normal subjects.

The mean duration of the first agonist burst for all 13 patients was not sig-
nificantly different from that in normal subjects (not illustrated). However, the
duration of the first agonist burst in patients who were rigid was prolonged when
compared with normal subjects (ANOVA at 15° and 60°, F (1, 9) = 15.14, P < 0.01)
(fig. 4). Similarly, prolongation of the first agonist burst also was present in those
patients with severe chorea compared with normal subjects (ANOVA at 15° and
60°, F (1,10) = 6.52, P<0.05) (fig. 4). There was no difference in the duration of the
first agonist burst in those patients with chorea who were receiving neuroleptic
drugs and those who were not (ANOVA at 15° and 60°, F (1,8) = 1.72, P>0.05).
The duration of the first agonist burst was highly variable in all patients (fig. 2C, D).

In 3 patients (Cases 15–17) with severe chorea in whom it was not possible to
measure the EMG activity, a well defined agonist burst, representing the initial
component of the normal biphasic pattern of agonist and antagonist muscle

![Graph showing duration of first agonist burst (Agl) in wrist flexor muscles during wrist flexion movements of amplitudes 15° and 60° in 8 normal subjects (open bars) and 13 patients with Huntington’s disease (hatched bars). The patients have been divided on clinical grounds into three groups. The Agl duration of akinetic-rigid patients and patients with severe chorea were longer than normal (for comparison of the duration of Agl for 15° and 60° movements in patients versus normal subjects (ANOVA): *P<0.05, **P<0.01).]
activation, was only seen occasionally. The agonist burst was often poorly defined, varying from a single prolonged and dispersed burst of activity to repeated smaller bursts. Activity in the agonist muscle occurred both in isolation and in combination with an antagonist burst of variable timing, either cocontracting or starting before or after the agonist. These different patterns could be recorded in the same patient on successive trials.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Position</th>
<th>Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps</td>
<td>FF</td>
<td>10°</td>
</tr>
<tr>
<td>Triceps</td>
<td>FF</td>
<td>200°/s</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>FE</td>
<td>0.1 mV</td>
</tr>
<tr>
<td>R. tibialis anterior</td>
<td>FF</td>
<td>0.1 mV</td>
</tr>
<tr>
<td>R. triceps surae</td>
<td>FE</td>
<td>0.1 mV</td>
</tr>
<tr>
<td>L. tibialis anterior</td>
<td>FF</td>
<td>0.1 mV</td>
</tr>
<tr>
<td>L. triceps surae</td>
<td>FE</td>
<td>0.1 mV</td>
</tr>
</tbody>
</table>

**FIG. 5A.** EMG recordings from a variety of muscles in a 60-yr-old man with Huntington's disease and mild chorea (*Case 7*), while seated, illustrating the random pattern of muscle activation and variable EMG burst length of chorea. Fig. b, wrist position, angular wrist velocity traces and rectified EMG signals from forearm flexor (FF) and extensor (FE) muscles in a 40-yr-old woman with Huntington's disease illustrating a choreic burst interrupting an attempted voluntary wrist flexion movement to 15° (*left panel*) and spontaneous choreic movement producing a small amplitude movement (*middle and right panel*).
Involuntary movements

The EMG activity corresponding to spontaneous chorea was characterized by a random flow from one muscle group to another, and a highly variable duration of the individual choreic bursts. The duration of the great majority of choreic bursts ranged from 200 to 400 ms. However, a wide spectrum was present with short, discrete bursts of the order of 50 to 200 ms duration and prolonged contractions lasting up to 2 s (fig. 5A).

In 3 patients (Cases 4, 11, 13) it was possible to compare spontaneous choreic movements of the wrist with those produced by voluntary activity. The EMG activity in the forearm muscles during these spontaneous movements consisted of long cocontracting bursts in the agonist and antagonists (fig. 5B). These cocontractions produced movements of only small amplitude (1° to 20°). The angular velocity of these movements (20 to 400 deg/s) were comparable with speeds of voluntary movements for similar amplitudes in the same patients. The mean angular velocity of voluntary simple wrist flexion movements in the same patients varied from 15 to 336 deg/s. Often it appeared as if chorea interfered with the execution of normal voluntary movements. For example in fig. 5B, there was an initial correct movement to 15°, which was followed by an additional EMG burst which took the wrist beyond the target. In other subjects, the opposite occurred: a large antagonist burst displaced the wrist in the direction opposite to the target.

Complex voluntary movements

The two types of complex voluntary movements studied were (1) simultaneous isotonic flexion of the elbow and isometric squeeze of a force transducer, and (2) a sequential movement of squeeze followed by flexion. As with the simple wrist flexion task, all movements were self-paced and executed with the instruction to be made as fast as possible.

Simultaneous flex and squeeze. Normal subjects performed this simultaneous movement task with ease. The peak velocity and timing of the individual components of flex and squeeze were the same as when the individual movements were performed separately (fig. 6).

Of the 6 patients who were examined (1 was receiving a neuroleptic drug), only 2 performed as normal. When each component (flex and squeeze) was carried out separately by these 2 patients, their individual movements were as fast as normal. Their peak velocity and movement time did not change when the two movements were executed simultaneously. These patients (Cases 7, 10) had mild chorea with little functional impairment (both were taking baclofen).

In the remaining patients (Cases 4, 5, 9, 13), the movement times for the simple single squeeze movement were prolonged (mean (± 1 SD) movement time 406 ± 132 ms; normal subjects 156 ± 23 ms, \( P < 0.001 \)), as were those for simple single elbow flexion (mean movement time 399 ± 124 ms; normal subjects 229 ± 41 ms, \( P < 0.001 \)). When performed simultaneously, the squeeze movement
FIG. 6. Movement times for elbow flexion (MTFL) in 10 normal subjects (right hand panel) and 6 patients with Huntington's disease (left hand panel) when performed alone (simple) and simultaneously with a squeeze movement of the hand (simultaneous). In 4 of the 6 patients with Huntington's disease, performance of the simultaneous task led to a marked slowing and prolongation of the elbow flexion movement time. Normal subjects (and 2 patients) were able to perform the simultaneous task without any decay in movement times. One patient was receiving a neuroleptic drug, pimozide, and is shown by solid symbols; 3 others were taking baclofen and 2 were untreated. * akinetic-rigid; b mild chorea; c severe chorea.

time remained unchanged, but the elbow flexion movement became slower and the movement time increased (from 399 ± 124 ms to 904 ± 216 ms, *P* < 0.001). Two of these patients (Cases 5, 9) had mild chorea, 1 of whom (Case 5) was receiving baclofen; 1 had severe chorea (Case 13) and was receiving pimozide, and 1 was akinetic and rigid on no therapy (Case 4).

Sequential squeeze then flex. Normal subjects executed each component movement of this task as rapidly as when each movement was made separately. There was a slight pause between the completion of squeeze and the onset of the flex movement lasting 94 ± 12 ms; the mean interonset latency between the movements was 244 ± 33 ms.

When attempting to perform sequential movements, profound difficulties were observed in the 5 patients studied (Cases 4, 5, 7, 9, 13). All found this task difficult to learn. One patient (Case 9) with mild to moderate chorea, who was not on treatment, was unable to perform the task, while another (Case 7), again with mild to moderate chorea and only taking baclofen, could only perform the two movements simultaneously. The remaining 3 patients (Case 4 on no treatment, Case 5 only taking baclofen, and Case 13 on pimozide) had squeeze movement times that were the same as those when this movement was performed alone. However, the elbow flexion movement times in the sequence exceeded those when this movement was performed alone (by 226, 68 and 1007 ms, respectively). The
IOL between the two movements of the sequence was significantly longer in these subjects (452, 504 and 628 ms, respectively; mean 528 ± 90 ms) than in normals (244 ± 33 ms, P < 0.001), as was the pause (223, 190 and 244 ms, respectively; mean 219 ± 27 ms) as compared to normals (94 ± 12 ms, P < 0.001).

**Stretch reflexes**

*Wrist flexors.* The average latency, duration and size of the short and long-latency components of the stretch reflexes in the flexors of the wrist obtained in the 12 normal subjects and the 17 patients with Huntington's disease are shown in fig. 7. Short-latency reflexes were present in all normal subjects and patients, and long-latency responses were present in all normal subjects, and in 15 of the 17 patients. Both patients in whom the reflex was absent had severe chorea.

![Fig. 7](image-url)  
*Fig. 7.* Mean (± SD) size, duration and latency of short (SLR) and long-latency (LLR) stretch reflexes in wrist flexor muscles (WF), and long-latency stretch reflexes (LLR) in flexor pollicis longus (FPL) in normal subjects (open bars) and patients with Huntington's disease (hatched bars). Short-latency EMG responses to stretch were present in the flexor muscles of all normal subjects (n = 12) and patients (n = 17); long-latency responses were present in all normal subjects in both the wrist flexors and flexor pollicis longus, but were absent in the wrist flexor muscles in 2 patients and in flexor pollicis longus in 9 of the 15 patients in whom it was possible to examine this reflex (upper left panel). The latency of the long-latency reflexes in the wrist flexor and flexor pollicis longus muscles were longer than normal (upper right panel), and the duration of both short and long-latency stretch reflexes were prolonged (lower left panel) in patients with Huntington's disease. The size of the long-latency components were smaller than normal (lower right panel) but this was significant only for the wrist flexors. Response size has been expressed as the fractional increase in EMG activity above baseline. *P < 0.05, **P < 0.01, ***P < 0.001.*
The size and latency of the short latency responses in patients were similar to normal, but their duration was prolonged ($P<0.01$). The mean size of the long-latency responses was smaller than normal ($P<0.01$) while the mean duration ($P<0.05$) and mean latency ($P<0.01$) were prolonged in patients. The duration of the long-latency reflex was longer in patients with mild and severe chorea than in those who were akinetic and rigid (akinetic-rigid vs mild chorea, $P<0.05$; akinetic-rigid vs severe chorea, $P<0.01$). There was no difference in the size or latency of the reflexes between the patients with respect to medication.

*Flexor pollicis longus.* Short-latency stretch reflexes cannot be obtained from the thumb in many normal subjects, so only long-latency reflexes (which were present in all normal subjects) are considered. Two patients (Cases 1,17) were unable to maintain a constant position of the thumb. In 9 patients (Cases 6, 7, 9–11, 13–16) the long-latency EMG responses were absent, although they had been present in the wrist flexors in 7 of these patients. In 6 other patients (Cases 2–5, 8, 12) long-latency reflexes in flexor pollicis longus were present; with one exception, these patients had mild chorea or were akinetic and rigid.

The average latency, duration and amplitude of the long-latency EMG response to stretch of the flexor pollicis longus in normal subjects and in the 6 patients with Huntington’s disease are shown in fig. 7. In those in whom the reflex was present the latency was delayed ($P<0.001$), and the mean duration was prolonged in comparison with normal subjects ($P<0.05$), but there was no difference in the size of the response ($P<0.05$). There were insufficient numbers to allow a comparison of the patients with and without drugs.

*Cortical somatosensory evoked potentials*

The first 3 components of the cortical SEP (N1, N1-P1, P1-N2, see Methods) following median nerve stimulation at the wrist were examined in 16 of the 17 patients. Potentials recorded over Erb’s point and the cervical spinal cord were of normal latency (Erb’s point $9.8 \pm 0.9$ ms (mean $\pm 1SD$); normal $10 \pm 0.6$ ms; cervical spine $13.2 \pm 1.3$ ms; normal $13.3 \pm 0.8$ ms). No cortical response could be distinguished in 7 patients (Cases 2, 10, 13–17). The sizes of all 3 components of the cortical SEPs in the total group of patients were significantly smaller than normal (Mann-Whitney test, $P<0.05$). In 9 patients (Cases 1, 3–9, 11, 12) in whom a cortical potential was obtained the mean N1 latency was normal ($19.8 \pm 1.7$ ms; normal $18.9 \pm 0.7$ ms), but the size of N1 and N1-P1 components were smaller than normal (Student’s t test on the logarithmically transformed data, $P<0.002$). However, the amplitude of the P1-N2 component was the same in both groups ($P>0.05$) (Table 2).

As was noted with the long latency stretch reflex in the thumb flexor, the cortical SEP was absent in most patients with severe chorea (Table 1). However, using a $\chi^2$ analysis, there was no association between the presence or absence of the long-latency stretch reflex in flexor pollicis longus and the SEP ($\chi^2 = 1.7, df = 1, P>0.05$).
TABLE 2. SUMMARY OF SEP LATENCY AND AMPLITUDE MEASUREMENTS. THE AMPLITUDE (MEAN ± 1 SD) OF THE SEP COMPONENTS GIVEN FOR THE 9 PATIENTS IN WHOM SEP WAS PRESENT*

<table>
<thead>
<tr>
<th>Component</th>
<th>Normal subjects (n = 11)</th>
<th>Huntington's disease (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 latency (ms)</td>
<td>18.9 ± 0.7</td>
<td>19.8 ± 1.7</td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>1.4 ± 0.8</td>
<td>0.34 ± 0.33</td>
</tr>
<tr>
<td>Log</td>
<td>0.0904 ± 0.2444</td>
<td>-0.5431 ± 0.4892**</td>
</tr>
<tr>
<td>N1-P1</td>
<td>2.8 ± 1.2</td>
<td>1.3 ± 1.2</td>
</tr>
<tr>
<td>Log</td>
<td>0.4013 ± 0.2113</td>
<td>-0.1087 ± 0.2684**</td>
</tr>
<tr>
<td>P1-N2</td>
<td>1.9 ± 1.1</td>
<td>2.1 ± 2.4</td>
</tr>
<tr>
<td>Log</td>
<td>0.2476 ± 0.1924</td>
<td>0.2312 ± 0.3964</td>
</tr>
</tbody>
</table>

* For details of SEP component labelling and identification, see Methods.
** P < 0.002.

We then sought to investigate whether the size of the long-latency stretch reflexes in each muscle were related to the size of the SEP components, but no relationship could be found (Spearman rank correlation coefficients (ρ): size of long-latency stretch reflex in wrist flexors (n = 16) vs size N1, ρ = 0.1; vs size N1-P1, ρ = 0.01; vs size P1-N2, ρ = 0.02; size of long-latency stretch reflex in flexor pollicis longus (n = 14) vs size N1, ρ = 0.5; vs size N1-P1, ρ = 0.4; vs size P1-N2, ρ = 0.4; P > 0.05 for all values).

There was a marginal association between the presence or absence of the long-latency stretch reflex in flexor pollicis longus and the clinical assessment of chorea in the 3 groups of patients (χ² = 5.97, df = 2; P = 0.05), but none was evident for the SEP (χ² = 3.1, df = 2, P > 0.05).

Finally, we attempted to test whether there was any correlation between the SEP, long-latency stretch reflexes and the speed of voluntary movements in individual patients. There was no correlation between any component of the SEP or of the size of the stretch reflex in wrist and thumb flexors and the peak velocity of a 60° wrist flexion movement (Spearman rank correlation coefficients (ρ): velocity (n = 12) vs size N1, ρ = 0.2; vs size N1-P1, ρ = 0.1; vs size P1-N2, ρ = 0.1: velocity vs size wrist flexor long-latency stretch reflex, ρ = 0.2; vs size flexor pollicis longus long-latency stretch reflex, ρ = 0.3: P > 0.05 for all measurements).

DISCUSSION

The present experiments revealed abnormalities of motor control and the processing of sensory information in patients with Huntington's disease. The latter have been well documented previously, but it has not been clear whether or how they might be related to the major clinical motor manifestations of the disease. The
problems that are encountered in interpreting these findings are addressed below, followed by a discussion of the new findings in this study concerning the control of voluntary movement.

**Sensory processing in Huntington’s disease**

The changes that we have documented in the long-latency stretch reflex and in the somatosensory evoked potentials are very similar to those described previously (see Ehle et al., 1984; Noth et al., 1984; Bollen et al., 1985). Both the primary component (baseline – N1 peak, or N1-P1) of the median nerve evoked potential, and the long-latency stretch reflex in forearm muscles, tended to be reduced in size or absent in patients with Huntington’s disease. In addition, we have shown (1) that the effect on the long-latency stretch reflex is greater on the long flexor of the thumb than on the flexor muscles of the wrist in the forearm, and (2) that although the primary component of the SEP is abnormal, the later P1-N2 peak may be unaffected in the patient group.

The reasons for these electrophysiological abnormalities are not known in detail. Absence of the N1 component of the SEP may reflect a failure or a desynchronization of the afferent input reaching the cerebral cortex. This must be presumed to occur above the level of the generators of the spinal SEP components as these were normal, and could result from pathological processes affecting the cortex (Bollen et al., 1985) or thalamus (Ehle et al., 1984), both of which are known to be involved in Huntington’s disease. If the P1-N2 component of the SEP is due to later long-term processing of the input responsible for the N1 peak, then desynchronization of the primary input might have less effect on the P1-N2 response and account for its relative preservation in the patients.

Absence or reduction of the long-latency component of the stretch reflex might also be compatible with changes in sensory input to cortex. If a long loop transcortical reflex pathway does contribute to the long-latency stretch reflex (Marsden et al., 1983a), then it would not be surprising to find that the reflex is reduced in a group of patients with evidence of abnormal sensory input to cortex. The hypothesis that the transcortical loop plays a more important role in reflex responses of muscles controlling the most distal joints of the hands (see Marsden et al., 1983a) would also account for the more pronounced changes in the flexor pollicis longus, compared with the wrist flexor stretch reflexes. If these changes in long-latency stretch reflexes are explained by involvement of a transcortical pathway, it might be expected that there would be a correlation between the size of the SEP and the reflex, especially as about 50% of the primary component of the SEP is due to activity in muscle spindle 1a afferent projections (Gandevia et al., 1984). However, the absence of a correlation was not altogether surprising. The reason for this is that the SEP was obtained by stimulation of afferents (median nerve at wrist) which could not have contributed to the stretch reflex of the muscles studied. Ideally, the SEP should be recorded in response to stretch of a single muscle and correlated with the resulting long-latency stretch reflex in the same muscle.
Despite the relatively clear abnormalities in the SEP and stretch reflex, we still do not know how they relate to the difficulties experienced in voluntary movement in Huntington's disease. Neither the long-latency stretch reflex nor the SEP changes were significantly correlated with measures of voluntary movement or the clinical grouping of the patients (mild chorea, severe chorea or akinetic-rigid). They appeared to be epiphenomena of the disease process rather than casual factors in the clinical picture. However, the numbers of patients in each group were small; correlations between electrophysiological abnormalities and clinical symptoms may become apparent in future studies with larger groups of patients. One possibility is that the size of the long-latency stretch reflex might be related to the muscle tone in Huntington's disease, as it is in Parkinson's disease (Lee and Tatton, 1975; Rothwell et al., 1983). If so, it would pose an interesting question for longitudinal study: do patients who lose the long-latency stretch reflex in the mild to moderate middle stages of the disease regain it during the final rigid phase? Or do patients who become rigid belong to a separate group of individuals who never lose their stretch reflex?

Voluntary movement in Huntington's disease

Three major abnormalities of voluntary arm movement in patients with Huntington's disease were studied. (1) The maximum speed of voluntary wrist flexion was reduced compared with normal subjects. Hefter et al. (1987) have reported a similar slowness of rapid finger movements in Huntington's disease. Such slowness of movement attempted at maximum velocity was most obvious in akinetic-rigid patients, but was also seen in those with chorea alone. It was not due to the effects of neuroleptic treatment; those patients who were receiving medication moved as fast as those who were drug free. (2) Combined simultaneous or sequential movements of 'squeeze' of the hand and 'flex' of the elbow were even more affected. Many patients were unable to execute such movements. In those who could, the speed of elbow flexion often was further reduced when executed at the same time or shortly after a hand squeeze. Similarly, the pause between component movements during the sequential task was longer than normal. These defects of complex movements were seen in those with chorea alone, and in those not taking neuroleptic drugs. (3) All voluntary movements to a target were more variable in both the final end position and the peak velocity than the movements of normal subjects.

Bradykinesia in Huntington's disease

The first two deficits are very similar to those seen in patients with Parkinson's disease, and reflect an underlying bradykinesia in Huntington's disease. Not surprisingly, the degree of bradykinesia was greatest in patients who were akinetic and rigid, but it was also seen in those with chorea alone, especially those with severe chorea. Such bradykinesia occurred in those not taking neuroleptic drugs, so cannot be attributed to drug-induced parkinsonism. We conclude that
bradykinesia is a fundamental feature of the motor deficits of Huntington's disease, even in those who clinically appear only to have chorea.

Clinical studies of Huntington's disease indicate that difficulties with voluntary movement become more pronounced as chorea subsides and bradykinesia becomes more evident. This would explain why neuroleptic treatment may produce little improvement in functional ability despite pronounced effects on chorea (Shoulson, 1981; Girotti et al., 1984; Quinn and Marsden, 1984; Koller and Trimble, 1985). Indeed neuroleptic therapy may make matters worse by exaggerating bradykinesia.

Slowness of fast simple single voluntary movements is characteristic of Parkinson's disease (Hallett and Koshbin, 1980; Berardelli et al., 1986). So too is disruption of complex dual simultaneous and sequential movements (Benecke et al., 1986, 1987). Similar defects of both simple and complex movements were found in Huntington's disease in the present study. In both conditions, complex movements appear more affected than simple tasks. Thus patients with Huntington's or Parkinson's disease are capable of executing simple single movements in the correct direction, albeit more slowly than normal, and can adjust their motor output to achieve movements of different sizes. However, when they attempt to execute more complex simultaneous or sequential motor acts, added difficulties emerge. A further slowing of the second movement appears and its initiation is delayed. This suggests that there is a difficulty in motor programming of complex movements in both diseases, over and above the defect in execution of single simple movements.

Although superficially similar in terms of its effect on movement speed, the detailed mechanism of bradykinesia in Huntington's disease may be different from that in Parkinson's disease. The slowing of voluntary movement in the mild and severe choreic groups was not accompanied by any other clinical signs of parkinsonism. In addition, the EMG patterns recorded during voluntary wrist flexion, even in those patients who were akinetic-rigid (i.e., clinically parkinsonian), were not the same as those seen in Parkinson's disease (Hallett and Khoshbin, 1980; Berardelli et al., 1986). In the latter disorder, the first burst of activity in the agonist is small but of normal duration, in contrast to the prolonged and highly variable EMG bursts of Huntington's disease. Prolonged EMG bursts and variable movement trajectories are more reminiscent of those described in athetosis (Hallett and Alvarez, 1983) and Sydenham's chorea (Hallett and Kaufman, 1981). Nevertheless, despite these detailed differences, the final bradykinesia for both simple and complex simultaneous and sequential movements is remarkably similar in both Huntington's and Parkinson's disease.

The corticomotoneuron pathway appears normal in both Parkinson's and Huntington's disease (Thompson et al., 1986), so the defects of motor programming seen in both conditions probably lies in delivery of abnormal motor instructions to the motor cortex from premotor and supplementary motor cortical areas. Abnormal motor programming in both Parkinson's and Huntington's disease is best interpreted as due to dysfunction of the premotor and supplementary motor
Contemporary theories of basal ganglia motor function concentrate upon an input from motor cortex (excitatory) to striatum, a striatal output (inhibitory) to medial globus pallidus and substantia nigra pars reticulata, then pallidal and nigral outputs (inhibitory) to thalamus VA and VL, and thalamic projections (excitatory) to premotor and supplementary motor areas (Kemp and Powell, 1971; Penney and Young, 1983; Alexander et al., 1986). This cortico-striato-pallido/nigro-thalamo-cortical feedback loop is excited by cortical input, and results eventually in facilitation of premotor and supplementary motor cortical activity. In other words, input from the sensorimotor cortex facilitates activity in the premotor areas through this complex basal ganglia motor circuit, which acts as a positive feedback system that might reinforce ongoing motor activity.

Loss of striatal output neurons in Huntington’s disease would remove basal ganglia activation of premotor areas. The situation in Parkinson’s disease is more complex. At first sight, loss of dopamine inhibition of striatal neurons might be expected to facilitate basal ganglia excitation of the cortex, that is, the opposite of what happens in Huntington’s disease. However, recent evidence (see Penney and Young, 1986) suggests that the overall effect of dopamine is excitatory to striatal output neurons to medial globus pallidus and substantia nigra reticulata. Accordingly, loss of the dopaminergic nigral pathway to the motor areas of the striatum in Parkinson’s disease might have a similar functional effect as the loss of those striatal output neurons in Huntington’s disease. The bradykinesia characteristic of Parkinson’s disease, and now shown to be a fundamental motor deficit in Huntington’s disease, would thus be due to impairment of activity in the cortico-striato-pallido/nigro-thalamo-cortical motor circuit in both conditions, leading to a failure of activation of premotor and supplementary motor cortex.

**Chorea in Huntington’s disease**

The cause of the choreic movements in Huntington’s disease remains unknown. The variable duration of the bursts of muscle activity in chorea and their random timing and distribution are well-known clinical characteristics (Wilson, 1925; Hoefer and Putnam, 1940; Hallett and Kaufman, 1981; Marsden et al., 1983b). There are therefore no specific EMG characteristics that define individual bursts of EMG activity as chorea: they may be of short duration as in myoclonus, or long as in dystonia (Marsden et al., 1983b). In this study we have shown that choreic movements tend to be of small amplitude and of low velocity, similar to voluntary movements of comparable amplitudes in the same patients.

Building upon the critical function of the cortico-striato-pallido/nigro-thalamo-cortical motor circuit in reinforcing motor behaviour, Penney and Young (1983, 1986) have highlighted the parallel role of cortico-striato-pallido-subthalamo-pallidal pathways in inhibiting movement. Cortical inputs excite striatal neurons that inhibit lateral globus pallidus, which projects an inhibitory pathway to the
subthalamic nucleus. The end effect of this cortical input would be to drive subthalamic activity, reinforced by a direct excitatory corticosubthalamic pathway. It is suggested that the subthalamus projects excitatory pathways to the medial globus pallidus to suppress unwanted movement.

The important role of the subthalamic nucleus in the production of dyskinesias is supported by observations made on lesions in the region of the subthalamic nucleus, which produce contralateral hemiballism or hemichorea (Martin, 1927; Whittier, 1947; Crossman et al., 1984). Injections of bicuculline into the subthalamic nucleus or ventrolateral lentiform nucleus, in the monkey, can produce hemiballism or hemichorea, respectively (Mitchell et al., 1985a, b). Although the mechanisms responsible for these experimental dyskinesias are unresolved (see Crossman, 1987, for recent review), local cerebral metabolic activity after such injections (examined by 2-deoxyglucose autoradiography) in both hemiballism and hemichorea showed changes consistent with decreased activity in subthalamopallidal and pallidothalamic pathways (Mitchell et al., 1985b; Crossman, 1987).

Loss of striatal neurons in Huntington's disease would have the same effect, causing disinhibition of lateral globus pallidus projections to the subthalamic nucleus, which would be excessively inhibited. The loss of subthalamic drive to medial pallidal neurons would result in decreased pallidothalamic inhibition causing increased thalamocortical excitation, thereby generating chorea. Although speculative, such a theory predicts that bradykinesia and chorea can coexist, as has been found in the present study.

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