

Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease?

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Summary

The aim of this study was to see whether action tremor contributes to the weakness which can be measured in some muscles in patients with Parkinson's disease, by preventing fully fused contraction of motor units. Strength and action tremor were recorded during maximal wrist extension in patients when they were on and off antiparkinsonian medication, and in age- and sex-matched healthy subjects. Peak torque and mean rectified EMG levels were reduced by 25% and 30% ($n = 7$), respectively, when patients were off medication (compared with when they were on medication). In parkinsonian patients off treatment, action tremor was visible in torque and EMG records, and had a frequency of ~10 Hz. The absolute amplitude of this tremor was considerably smaller in patients on medication and in control

subjects. In patients, medication reduced action tremor in torque and EMG by 37% and 57%, respectively, so that tremor amplitude approached that in normals. Similar changes were seen when action tremor was expressed as % peak torque or % mean rectified EMG. In parkinsonian patients off medication, a 10-Hz synchronizing influence dominates muscle activity at the wrist. The result is an incompletely fused muscle contraction, which is an important factor contributing to the weakness present in the off-medication state. Antiparkinsonian medication releases motor units from the 10-Hz synchronizing influence, enabling higher discharge rates, fused contraction and improved force generation.

Keywords: Parkinson's disease; action tremor; weakness

Abbreviation: ISI = interstimulus interval

Introduction

There is a growing body of evidence that patients with Parkinson's disease may be weak in some muscle groups, even when allowance is made for the slow development of maximal force (Stelmach *et al.*, 1989; Yanagawa *et al.*, 1990; Logigian *et al.*, 1991; Corcos *et al.*, 1996). In particular, we recently reported that elbow-extension torque is reduced when patients are off antiparkinsonian medication, compared with when they are on it (Corcos *et al.*, 1996).

The reasons for this weakness are unclear. Several authors have drawn attention to the tendency of motor units to discharge synchronously with a 10-Hz rhythm during voluntary activity in parkinsonian patients (Hoefler and Putnam, 1940; Lance *et al.*, 1963; Teravainen and Calne, 1980). This leads to an action tremor, separate from the more usual rest tremor seen in these patients (Lance *et al.*, 1963).

Here we show that maximal voluntary wrist extension is weak in patients off antiparkinsonian medication, and we make two additional novel observations. First, action tremor persists during maximal voluntary extension of the wrist. The synchronization of motor unit activity to this 10-Hz rhythm inevitably limits the ability to generate a fused muscle contraction, leading to reduced strength. Secondly, action tremor is reduced by antiparkinsonian medication, so that motor units are free to discharge at high rate; this leads to a more fused and stronger contraction.

Patients and methods

Recordings of maximal wrist extension were made in seven patients with Parkinson's disease, when they were on

Table 1 Patient details

Patient	Age (years)	Disease duration	UPDRS [†]		Medication [‡]	Drug withdrawal period (h)
			On medication	Off medication		
1	73	6	23	27	Std L-D	18
2	50	10	15	32	Std and CR L-D, Lis	12
3*	46	9	17	48	Std and CR L-D, Sel, Amit	6
4	57	19	8	39	Std L-D, Sel, Am	12
5	51	4	12	44	Std and CR L-D, Sel	6
6	52	8	10	44	Std and CR L-D	18
7*	48	12	9	29	CR L-D, Amit, Sel	18

*Worst affected hand was tested in each case; in these two subjects this was the left hand. [†]UPDRS (Unified Parkinson's Disease Rating Scale) total maximum score 108. [‡]L-D = L-dopa plus decarboxylase inhibitor; Amit = amitriptyline; Std = standard preparation; Lis = Lisuride; CR = controlled release; Am = Amantadine; Sel = Selegiline.

antiparkinsonian medication and when they were off it. The clinical details of the subjects are summarized in Table 1. All the patients were right handed. Five cases had no resting tremor when they were on medication and two cases were free of resting tremor when they were off it. The worst affected hand was determined clinically and tested in each case (left hand in two cases). In each patient, all recordings were made on the same day (so that the same electrode position could be used when they were on and off medication). Wrist extension was also tested in seven age-matched healthy subjects (mean age 57.6 years, range 45 to 69 years). All patients and healthy subjects were male. Wrist extension was tested on the left in two controls. Healthy subjects had no clinical evidence of tremor. The studies were performed with the approval of the National Hospital for Neurology and Neurosurgery ethics committee and the informed consent of each subject.

Extension torque at the wrist was measured with the subject seated with his forearm pronated and held fixed on a table in front of him. The wrist was extended about 15° so that the dorsum of the hand made contact with a strain gauge suspended from above. Force was measured and then converted to torque using the distance between the point of contact between the wrist and strain gauge and the axis of the wrist (corrected for the 15° extension). The resonant frequency of the strain gauge was 80 Hz. During each run the patient was instructed to extend the wrist as hard as possible against the strain gauge with the fingers flexed at the metacarpophalangeal and interphalangeal joints.

In one experiment on a healthy control subject, the radial nerve was electrically stimulated where it re-enters the anterior compartment of the arm over the lower third of the humerus. Wrist extension torque was measured as above, with the exception that mechanical devices were used to limit shoulder movement or radial deviation of the wrist. Single shocks were 200 µs in duration and of sufficient intensity to elicit twitches in the forearm extensor muscles equivalent to ~5% of maximal voluntary torque. Submaximal shocks were used to limit discomfort and activation of local muscles (particularly biceps and brachioradialis) by local current spread. In order to ensure that the intensity of the

stimulus remained stable throughout the experiment, we continually verified that the twitch evoked by a single stimulus was of constant size. Five second trains of repetitive shocks with different interstimulus intervals (ISI) were then delivered as shown in Fig. 5. A pause of at least 120 s was given between trains.

Surface EMG was recorded with 9 mm diameter silver-silver chloride electrodes positioned over the forearm extensor muscles. Forearm extensor EMG and wrist torque were band-pass filtered at 1 kHz and a time constant of 3 ms. This time constant was chosen to limit any contribution of movement artifact to the 10-Hz peak in amplitude-frequency spectra. Signals were amplified and digitized with 12-bit resolution by a CED 1401-plus analogue-to-digital converter. The sampling rate was 2 kHz. The EMG was digitally rectified to determine mean EMG levels and prior to Fourier analysis. Signals were analysed by a software package (CED Spikedos). The fast Fourier transform was used to compute the discrete Fourier transform of blocks of data. Blocks were of equal duration, and spectra were estimated by averaging across blocks. Blocks were taken from the period of sustained torque, where the contraction was effectively isometric and local stationarity of the torque and EMG signals could be assumed. The non-cycling nature of data blocks was dealt with by applying a raised cosine window to each block, and then compensating for the resultant loss of power. This procedure may introduce some spurious power at very low frequencies, but the frequencies of interest were outside of this range.

From two to five practice trials were performed before recording, and patients were verbally encouraged to extend the wrist as hard as possible. Patients were given at least 1 min rest between trials. Torque and EMG were recorded during a further three trials of maximum extension in the off- and on-medication states. Contractions were maintained for at least 4 s beyond the point taken to reach 90% of peak torque measured in practice trials (for patients off medication, this point could be several seconds into the contraction). The trial with the maximum torque was selected for each drug state; the first 4 s of sustained torque (over which torque remained 90–100% of the peak torque) was then analysed. Amplitude spectra (1-Hz bin-widths) of torque and EMG

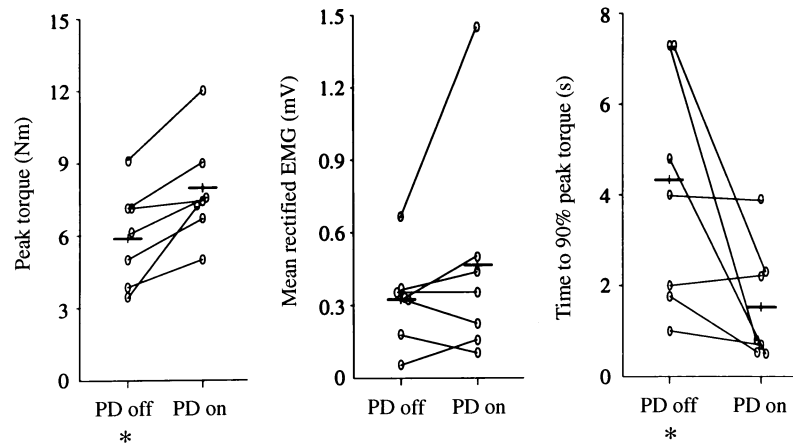


Fig. 1 Peak torque, mean rectified EMG and time to reach 90% peak torque during maximal wrist extension in patients with Parkinson's disease (PD) off and on antiparkinsonian medication. Peak torque significantly increased with treatment. Thick horizontal lines represent means. * $P \leq 0.05$ (off medication versus on medication).

were plotted for this period. Spectra of torque consistently showed a peak at ~10 Hz in parkinsonian patients and healthy subjects. The frequency and amplitude of this activity (sum of the amplitudes of the peak bin and of each bin either side) were measured using moveable cursors on a visual display. Parkinsonian patients off medication also showed a peak at ~10 Hz in amplitude spectra of EMG, but a clear peak was absent in three treated patients and in four controls. In these cases the three contiguous bins with the highest amplitude between 7 and 16 Hz were measured. Statistical analysis was performed using the Mann–Whitney, Wilcoxon and Spearman rank order correlation tests.

Results

Patients

The peak torque, mean rectified EMG level and time taken to reach 90% peak torque are shown in Fig. 1. There was a 25% reduction in torque when patients were off drugs. In addition, the mean level of rectified EMG during the period of sustained torque fell 30% when patients were off their antiparkinsonian medication. The time taken to reach 90% of peak torque increased by 271% when patients were off medication.

During maximal wrist extension, in patients off medication, torque records showed oscillations at ~10 Hz and the EMG had a tendency for segmentation into bursts at the same frequency. This 10-Hz action tremor could be present without a clinical rest tremor. However, the action tremor was absent or diminished in raw records of torque and EMG taken when the patients were on medication. Figure 2 gives the raw data records from Case 3. In it wrist extension is shown in the off- and on-medication states. The segmentation of the EMG and the 10-Hz fluctuation in the torque were far more evident when the patients were off medication. In this state, the unrectified surface EMG activity consisted of a series of

bursts with a peak-to-peak amplitude of up to 4.3 mV. When the patients were on medication, much higher frequencies prevailed in the EMG. In Cases 3 and 5, this consisted of a well-developed Piper rhythm, with rhythmic short duration bursts at ~40 Hz. These bursts had peak-to-peak amplitudes of up to 5 mV, and, like the action tremor bursts, represented synchronous activity in a large number of motor units. The corresponding torque fluctuations were small, presumably due to fusion of muscle twitches at higher frequencies.

Measurements of the amplitude and frequency of action tremor were taken from amplitude spectra of the torque and EMG waveforms during the period of sustained torque. Figure 3 shows the amplitude spectra for Case 2 when off and on medication. A large peak of activity at ~10 Hz is seen in the torque and EMG in contractions made when off treatment. On treatment, the 10-Hz peak in the torque spectrum is much smaller, and that in the EMG spectrum is no longer visible.

Frequency and amplitude data from the power spectra of patients and controls are summarized in Table 2 and Fig. 4. The frequency of the action tremor was ~10 Hz, and was not changed by medication. Figure 4A and B shows that the action tremor in torque and EMG was greater when the patients were off medication than in the same patients on medication, and greater than that in healthy controls (refer to Fig. 4 for statistics). Thus antiparkinsonian medication tended to reduce action tremor towards control values. This was paralleled by decreases in the relative tremor as illustrated in Fig. 4C and D. The relative tremor in torque and EMG was reduced by a mean of 56% and 51%, respectively in patients on treatment, compared with the off-medication state. There was no significant correlation between the absolute or relative reduction in action tremor and the increase in maximum torque in the on medication state. However, there was a correlation between the change in relative action tremor in the torque records and the percentage change in time to reach 90% peak torque ($r = 0.786$, $P = 0.039$).

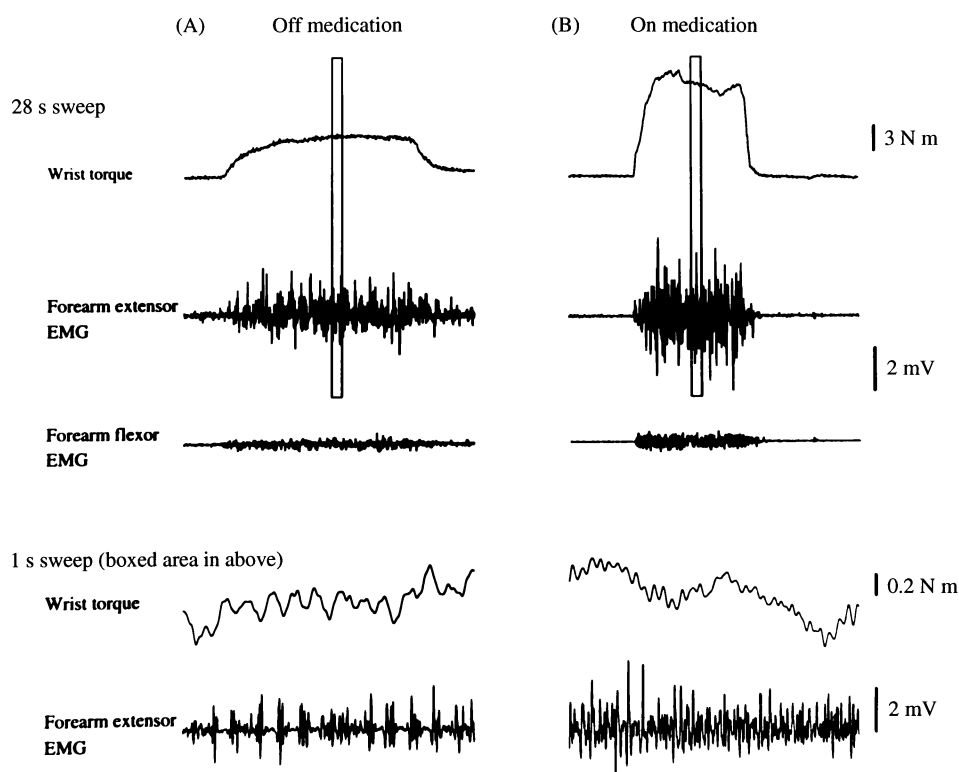


Fig. 2 Raw records of maximal wrist extension in Case 3. (A) Off antiparkinsonian medication; (B) on antiparkinsonian medication. Peak torque and EMG are greater on medication. The boxed area has been expanded in the lower two traces of A and B. In these, oscillations at 10 Hz are far more evident in the torque and EMG records for the patient off medication.

Healthy subjects

The peak torque during maximal wrist extension was 7.1 ± 0.5 N m (mean \pm SEM, $n = 7$). Subjects matched the patient groups in age, sex and arm tested. Amplitude spectra of the torque recorded during the period of sustained wrist extension demonstrated a peak with a frequency of ~ 10 Hz (see Table 2). A similar peak was recorded in spectra of EMG activity in only three subjects. The amplitude of the 10-Hz activity is shown together with the patient's results in Fig. 4.

Simulation studies of action tremor

The effect of action tremor on the torque generated by the forearm extensor muscles was simulated by electrical stimulation of the radial nerve of a healthy subject, with a train of shocks. The results are illustrated in Fig. 5. As expected a train at 10 Hz (Fig. 5A) generated a fraction of the torque produced by a train at 40 Hz (Fig. 5D). However, single motor unit studies in patients with Parkinson's disease suggest that motor unit discharges have a tendency to be paired (Das Gupta, 1963; Dietz *et al.*, 1974; Elek *et al.*, 1991). This is simulated in a normal subject in Fig. 5B by a 10-Hz train of double pulses (ISI = 25 ms). The torque generated is still lower than with a 40-Hz tetanus (Fig. 5D). The same is true even when the radial nerve is stimulated

with a 10-Hz train of quadruple pulses (ISI = 15 ms) so that the same total number of shocks is given as in the 40-Hz tetanus (Fig. 5C).

The contractions produced by trains of stimuli at 10 Hz are not fused, as can be seen from the tremor in the torque records (Fig. 5A–C). The amplitude of the tremor at the driving frequency was measured in the last second of each stimulus train. It was 33.0%, 7.9%, 1.8% and 0.1% of peak torque with 10-Hz trains of single, double and quadruple shocks, and a 40-Hz train of single pulses, respectively. Trains at 10 Hz, but not 40 Hz, elicited a slow ramp-like increase in torque over several seconds (compare Fig. 5A–C with Fig. 5D).

Discussion

We recently reported that elbow extension is weak in patients with Parkinson's disease when they are off medication (Corcos *et al.*, 1996). Here we extend these findings to extension at another joint, the wrist. The results add to a growing body of evidence that patients with Parkinson's disease may be weak even when allowance is made for their slow rate of force development (Stelmach *et al.*, 1989; Yanagawa *et al.*, 1990; Logigian *et al.*, 1991).

The question we address here is whether some of this weakness is caused by superimposed action tremor preventing

fused contraction of motor units and thus reducing maximal force output. We have shown that a 10-Hz action tremor can be recorded in torque and EMG during maximal extension at the wrist in parkinsonian patients off their treatment. This is likely to reflect a quantitatively important synchronization of motor unit activity at this frequency. For patients off medication, the relative amplitude of the 10-Hz tremor was ~2.5% of the peak torque. Given the low pass filter characteristics of muscle, including the partial fusion of contraction (Milner-Brown *et al.*, 1973; Allum *et al.*, 1978; Homberg *et al.*, 1986), the proportion of forearm extensor motor units synchronized to this rhythm must have been considerably >2.5%.

The experiment in which action tremor was simulated by trains of electrical stimuli delivered to the radial nerve provides useful information in this regard. In these experiments, all active units were synchronized to the same rhythm, and a 10-Hz train of single shocks gave a tremor in the torque signal which was ~30% of the maximum torque generated in the resulting contraction. This would imply that almost 10% (that is 2.5/30) of motor units were firing synchronously at 10 Hz in patients off their treatment. However, needle EMG studies in parkinsonian patients suggest that motor units fire more than once in each tremor burst (Das Gupta, 1963; Dietz *et al.*, 1974; Elek *et al.*, 1991). With a 10-Hz train of double shocks (ISI = 25 ms) to the

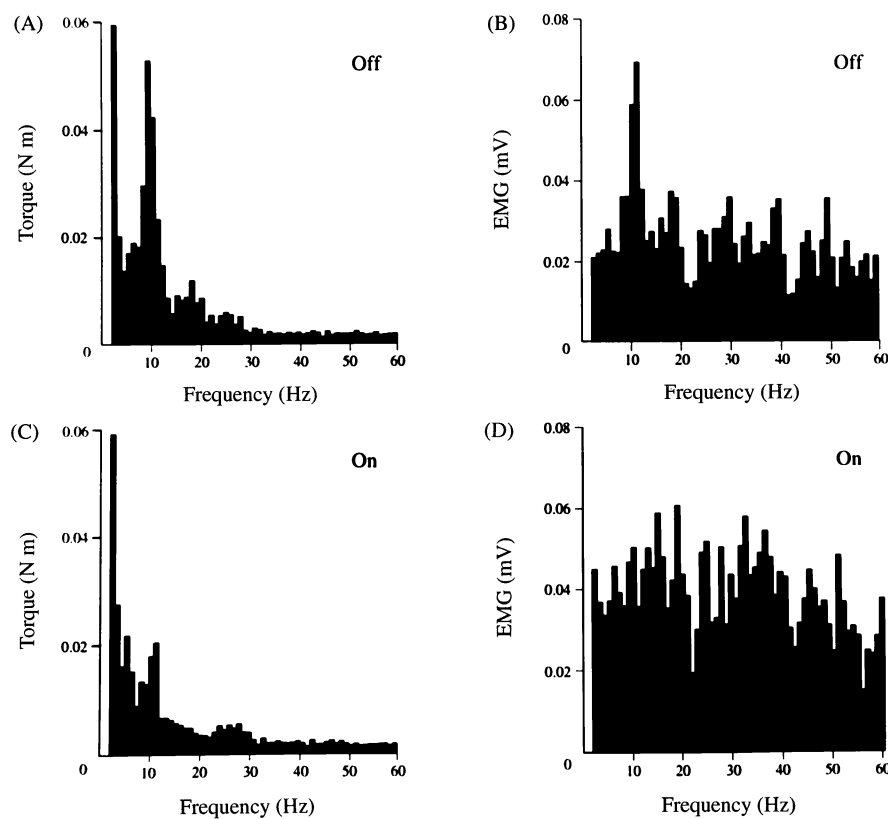


Fig. 3 Amplitude spectra of torque and EMG during periods of sustained contraction in Case 2 when off and on antiparkinsonian medication. A large peak is evident at around 10 Hz when off medication (**A** and **B**). This is reduced or absent when on medication (**C** and **D**). (Although the 10-Hz action tremor was the most striking feature of amplitude spectra of sustained torque, much smaller and less consistent peaks were sometimes evident at other frequencies in the on- and off-medication conditions.)

Table 2 Frequency of action tremor in maximal wrist extension

	Controls		Parkinson's disease patients			
	Frequency (Hz)*	(n)	On medication		Off medication	
	Frequency (Hz)*	(n)	Frequency (Hz)*	(n)	Frequency (Hz)*	(n)
Torque	10.7 ± 0.5	(7)	11.0 ± 0.9	(7)	10.1 ± 0.7	(7)
EMG†	11.3	(3)	10.6 ± 1.2	(4)	10.5 ± 0.7	(7)

*Mean ± SEM, where available. †Four normal controls and three patients on medication did not have a clear peak at ~10 Hz in amplitude spectra of EMG.

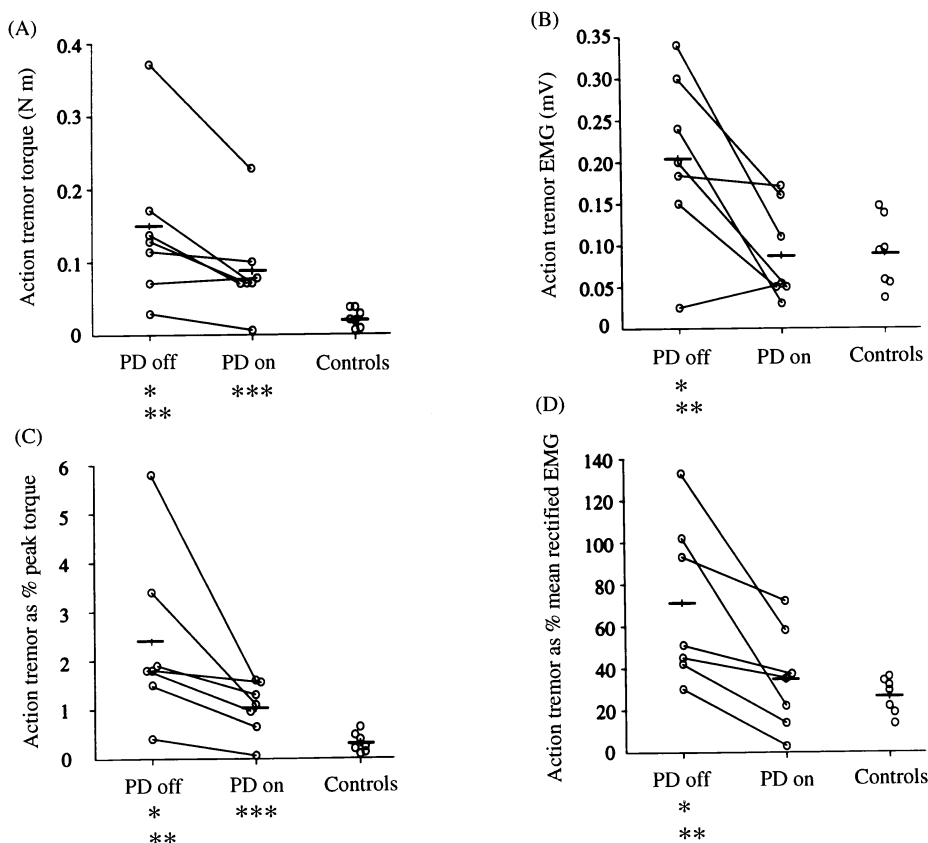


Fig. 4 Action tremor during maximal wrist extension in patients with Parkinson's disease (PD) off and on antiparkinsonian medication, and in age and sex matched healthy subjects. Absolute amplitude of 10-Hz action tremor is shown for torque and EMG in **A** and **B**. Relative action tremor, as a percentage of peak torque or mean rectified EMG, is shown in **C** and **D**, respectively. Both the absolute and relative amplitudes of the 10-Hz action tremor are reduced by treatment with dopaminergic drugs, so that they approach control values. Thick horizontal lines represent means. * $P \leq 0.05$ (PD off versus PD on); ** $P \leq 0.05$ (PD off versus controls); *** $P \leq 0.05$ (PD on versus controls).

radial nerve, tremor was around 8% of the maximum torque generated during contraction. If extrapolated to the patient results, the tremor of 2.5% peak torque for patients off medication suggests that around 30% (2.5/8) of motor units were locked to the 10-Hz rhythm. (The proportion of synchronized units would be even higher if individual units discharged more than twice in each tremor burst, or at intervals >25 ms.)

The appearance of the raw EMG also suggests that the proportion of motor units locked to the 10-Hz rhythm is considerable. Thus the EMG recorded during contractions in the off-medication state often consisted of a series of bursts, with little EMG activity between bursts. Overall action tremor accounted for ~70% of the mean rectified EMG activity during wrist contractions made when patients were off treatment (see Fig. 4D).

Thus a high proportion of the motor units involved in wrist extension are locked to a 10-Hz rhythm when patients are off medication. Under these circumstances contraction is not fully fused, and muscle strength will be impaired. Dopaminergic treatment reduced action tremor in both torque and EMG, so that it approached that measured in healthy

controls. In so doing, treatment releases motor units from the 10-Hz synchronizing influence so that units may then discharge at higher rates, as suggested by the development of a normal Piper rhythm in the EMG in two of our cases (Merton, 1981). In healthy subjects, powerful sustained contractions are usually associated with firing rates of 25–40 Hz (De Luca *et al.*, 1982; Bigland-Ritchie *et al.*, 1983; Marsden *et al.*, 1983). Higher discharge frequencies give fused or near fused contraction of motor units and thus greater force output. The effect is illustrated in Fig. 5.

The pathophysiological processes underlying the action tremor in torque and EMG are unclear. Parkinsonian action tremor may be due to an increase in the number of motor units firing together (Dietz *et al.*, 1974; Dengler *et al.*, 1986), through descending influences or segmental mechanisms such as the stretch reflex (Windhorst and Schweska, 1982), due to an increased number of motor units firing twice or more with each tremor beat (Das Gupta, 1963; Dietz *et al.*, 1974; Elek *et al.*, 1991), or due to a combination of these factors. Whatever the nature of those processes underlying the action tremor at the wrist, it is clear from the present results that they are under dopaminergic control.

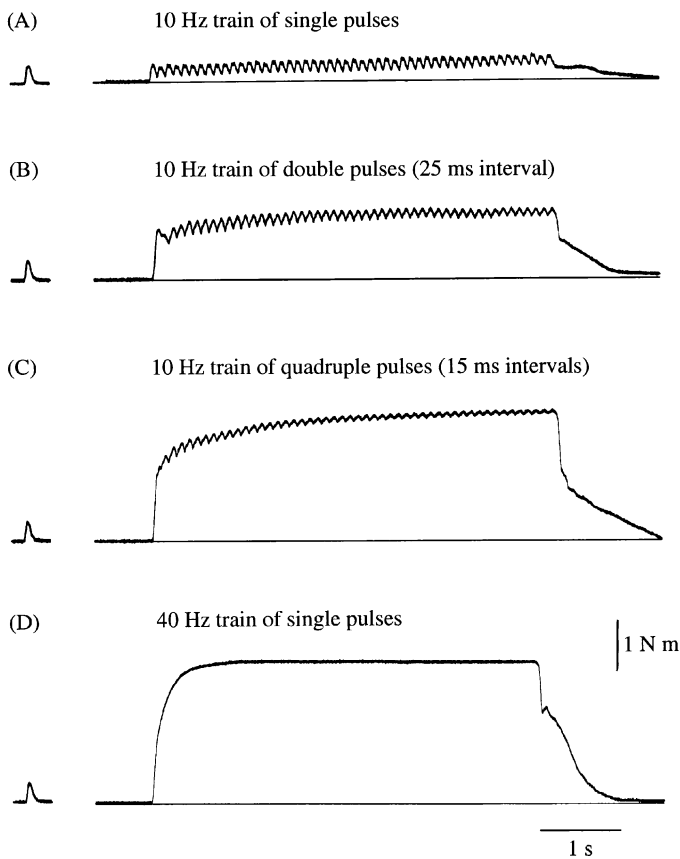


Fig. 5 Simulation of the effect of action tremor on wrist extension torque. The radial nerve was electrically stimulated in the upper arm in a healthy subject at rest. A series of single shocks was followed by a train of pulses. The torque generated by the two shocks preceding the train is superimposed to the left, and is more-or-less constant in **A**, **B**, **C** and **D**. The torque generated by each train of pulses is shown to the right. The torque produced by a train at 10 Hz (**A**–**C**) is less than at 40 Hz (**D**), whether each pulse in the 10-Hz train is single (**A**), double (**B**) or quadruple (**C**). There is a slow ramp-like increase in torque over several seconds in **A**–**C**, but not in **D**. Note the 10-Hz tremor present during contraction in **A**–**C**, (most evident in the first half of contraction). The slow return to rest at the end of each train is due to voluntary movement.

It is worth noting that the dominance of the action tremor at the wrist, when the patients are off medication, may contribute to the striking bradykinesia seen during extension as well as to the reduction in torque. Marsden and Meadows (1970) showed that a long series of shocks at 10 Hz delivered to a peripheral nerve leads to a slow ramp-like increase in muscle tension over the course of several seconds, possibly due to an increase in twitch time so that muscle contraction becomes increasingly fused. The effect is illustrated in Fig. 5, and is seen with both 10-Hz trains of single and multiple shocks. The 'ramp effect' is absent with trains of higher frequency. The parallel with the parkinsonian records is clear. In the off-medication state a large proportion of the active motor units in the forearm extensors discharged synchronously with a frequency of 10 Hz evoking a ramp

effect. The reduction in action tremor on medication correlated with the reduction in bradykinesia.

An important question is whether or not any of the weakness at the wrist in patients off treatment is due to failure to recruit motor units into the contraction. Although the present study does not address this point directly, we think it is unlikely that there is any great impairment of recruitment in wrist extensors. Even in normal subjects, almost all motor units are recruited in distal muscles at force levels of ~50% maximum voluntary contraction (De Luca *et al.*, 1982). Since patients can achieve such levels when off therapy, and in the face of clear action tremor, we presume recruitment to be relatively well preserved. The situation may be different in more proximal muscles where recruitment of new units into a contraction persists at force levels of 90% maximal voluntary contraction (De Luca *et al.*, 1982). In such circumstances, weakness could be due to a combination of action tremor and/or failure of recruitment. Measurements of action tremor suggest that the latter may be a more important factor in explaining strength loss in the elbow extensors of parkinsonian patients off treatment (P.B., D.M.C. and J.C.R., unpublished observations).

Finally, it is unclear to what extent the present results can be extrapolated to other forms of tremor. Essential tremor most clearly parallels parkinsonian action tremor in frequency, and yet patients with essential tremor do not generally complain of weakness. From our hypothesis we would predict that the excessive motor unit synchronization found with postural contractions would not persist during maximal voluntary contraction in patients with essential tremor. Preliminary findings suggest that this is indeed the case (P.B., unpublished observations).

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