Correlation between tremor, voluntary contraction, and firing pattern of motor units in Parkinson's disease

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SYNOPSIS Patients with tremor of Parkinsonism show three characteristics of motor unit activity: rhythmic spontaneous resting discharge, abnormally low firing rates during voluntary contraction, and consistent differences in firing pattern between small and large motor units. Smaller units discharge once per tremor beat at weak contractions but change into bursts of two or three spikes per beat at stronger forces. Large units are later recruited and fire preferentially once per beat. The large tremor amplitudes can be partly explained by synchronization of unfused twitches of low frequency units which summate more powerfully than the partially fused contractions during physiological tremor, which is about twice as rapid. Tremor is strongly influenced by the force of voluntary contraction. It is strongest at rest or during weak muscular effort and with increasing force becomes continuously of higher frequency and smaller amplitude. Both changes are the consequence of increasing discharge rates of motoneurons at stronger contractions.

Tremor is the result of synchronization of motor units. Tremor of Parkinsonism has a considerably lower frequency and larger amplitude than physiological tremor. It is unclear whether these peculiarities of the tremor of Parkinsonism are mainly the consequence of population effects like a stronger synchronization of motoneurons or to changes of the firing properties of single units.

Little is known about the correlation between single motor unit discharges and tremor, since this kind of investigation has been limited for methodological reasons. Recordings from normal low impedance electromyography (EMG) electrodes result in interference of many units, at least during stronger muscular contraction, so that single unit activity cannot be measured exactly. These disadvantages can be overcome by the use of selective microelectrodes. The subsequent single motor unit study of patients with

Parkinsonism tremor shows that the tremor characteristics of this disease are mainly the consequence of pathological changes of single motor unit activity.

METHODS

Complete data are available for 29 hand and forearm muscles from 11 patients with Parkinsonian tremor. In these patients tremor was present at rest and during voluntary activity. For comparison 16 recordings from the corresponding muscles of seven normal subjects were analysed. Single muscle fibres from the long extensor muscles of the fingers and the first dorsal interosseous muscle were recorded by means of the Ekstedt-Stalberg type of multielectrode or by high impedance tungsten electrodes. Force was measured by a strain gauge registering on a voltmeter in front of the patient. In addition, force and the spike recording were fed into an interface (WDV, München) for analogue-to-digital conversion and triggering and then into an IBM 1130 computer for storage and on-line data processing.

Tremor frequency was calculated by measuring the number of positive peaks in the EMG at the predominant frequency over the period of one second.

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FIG. 1. Dependence of tremor frequency (left) and tremor amplitude (right) on isometric tension plotted for the first dorsal interosseous muscle (upper half) and the long finger extensors (lower half). Mean values from six patients with Parkinsonism.

These measurements were taken by hand from time histories of tremor force.

In the case of recordings from the finger extensor muscles, the arm was fixed to a support which allowed changes in the angle between hand and forearm in order to vary the length of this muscle. For a more detailed description and the computation of the histograms see Freund and Wita (1971).

RESULTS

INFLUENCE OF VARIATION OF ISOMETRIC TENSION ON TREMOR FREQUENCY AND AMPLITUDE Tremor frequency and amplitude were measured from the time histograms of tremor force during stepwise increasing isometric contraction. As shown

in Fig. 1, tremor frequency increases and tremor amplitude decreases with rising isometric tension. This is true for both the first dorsal interosseous and the finger extensor muscles. This reciprocity of tremor frequency and amplitude has already been described by Jung (1941). The increase in frequency is remarkable, so that for the range of contractions examined tremor frequency during strong contractions is approximately twice that during weak contractions. The frequency change is less and the amplitude change is more pronounced in the lower range of contraction. In addition, with increasing force the tremor becomes more regular with respect to frequency and amplitude.

FIG. 2. Influence of variation of joint position of the hand on tremor frequency (left) and amplitude (right). Mean values of six Parkinsonism patients.

INFLUENCE OF VARIATION OF MUSCLE LENGTH

The length of the extensor digitorum longus muscle was varied by changing the angle between hand and forearm from zero to 45° flexion and 45° extension. Figure 2 shows that neither frequency nor amplitude of tremor are affected by this kind of experiment. These results are in agreement with those of Hofmann (1962) and Lance *et al.* (1963) that variation of muscle length has little or no influence on the tremor of Parkinsonism.

RECORDING OF SINGLE MOTOR UNIT POTENTIALS

The synchronization of motor units is commonly accepted to be the basic mechanism underlying tremor. The functional significance of grouped discharges of single units for tremor generation is less clear. Double discharges of single motor units were observed frequently in routine electromyography of tremor patients and were described by Denny-Brown *et al.* (1935), Lefebvre and Scherrer (1952), Das Gupta (1963), and Renou *et al.* (1970). The common observation from our single fibre recordings was that at weakest muscular efforts most motor units discharge only once per tremor beat. During successively stronger contractions these low threshold units discharge twice or even thrice per beat. In addition, larger units become recruited which again start firing with single discharges but, in

contrast with the smaller units, do not, or only exceptionally, fire in bursts during further increasing force.

FIRING RATES

These changes in the discharge

FIG. 3. Firing rates of a sample of seven single muscle fibres recorded from five patients with Parkinsonian tremor (lower trace) and of 11 fibres recorded from seven normal subjects (upper trace) during increasing force. Force increments (abscissa) were measured with reference to the force at which the particular unit was recruited.

FIG. 4. Example of the variation of discharge pattern of a single muscle fibre recorded from the first dorsal interosseous muscle with tremor amplitude.

pattern of motor units have some disadvantages for the calculation of firing rates. If a motor unit changes from regular to grouped discharges the firing rate may in some cases double or take any other ratio although the accompanying change in force is only small. Plotting firing rate against force therefore reflects pattern changes rather than frequency modulation according to variation of force and therefore has no functional significance. As will be discussed later, the consequences of grouped firing for the contractile properties are such that calculating the burst repetition rate is more adequate than counting the total firing rate.

To bypass this difficulty, direct measurements of firing rates were made only with high threshold motor units which showed single discharges over the whole range of contractions tested. As an estimate of the 'basic frequency' of low threshold units, the burst repetition rate was determined by measuring the intervals between the first spikes of the bursts. Although the frequency modulation of small and large motor units is different in normal subjects (unpublished observation) it turned out that the discharge rates of high threshold units and the burst repetition rate of low threshold units were the same. They

were therefore plotted together as shown in the lower trace of Fig. 3 for a sample of seven muscle fibres recorded from the long finger extensor muscles of five patients with tremor of Parkinsonism. For comparison, the discharge rates of a sample of 11 muscle fibres recorded from seven normal subjects are plotted on the upper trace. Frequencies were plotted against incremental instead of total force, since otherwise motor units of different recruitment threshold could not be pooled together. The main difference between the two curves is that discharge or burst repetition rates of the patients are about half that of normal subjects. All differences are statistically highly significant. These differences in firing rate correspond to those between the frequencies of the tremor of Parkinsonism and physiological tremor. This correspondence is to be expected, since in both tremor forms spikes (or bursts) and tremor beats show a 1:1 ratio.

There are no significant differences between the firing rates of Parkinsonism patients with and without tremor, except the fact that frequency doubling by grouped discharge does not occur in patients without tremor. Abnormally low discharge rates seem to be a common feature of α -motoneurons in this disease.

FIG. 5. Frequency profile (a), isometric tension (b), first order interval histogram (c), and joint interval histogram (d) of a single muscle fibre recorded from the first dorsal interosseous muscle of a normal subject. Frequency was calculated as reciprocals of the single interspike intervals without smoothing or averaging. First order intervals (c) are the times between two successive action potentials. Abscissa: interval length in ms; ordinate: frequency of occurrence of the interval. Binwidth: 10 ms. Joint interval histogram (d): each point represents the length of two adjacent interspike intervals, where the value given on the abscissa corresponds to interval n and that on the ordinate interval $n+1$. Consecutively, the same procedure is repeated starting with interval $n+1$ until the whole spike train is analysed this way.

ANALYSIS OF FIRING PATTERN On the basis of their consistent differences in firing pattern the motor units in Parkinson's disease with tremor can be subdivided into two groups:

1. Small, low threshold motor units which start firing either during resting tremor or during weak muscular effort with normal regular discharges of low frequency (3–5/s) but change into bursts consisting of two or even three spikes per tremor beat during stronger voluntary contractions.

2. Large, high threshold units which discharge

regularly with one spike per tremor beat at all force levels.

We will first consider the discharge pattern of the smaller motor units. As already mentioned, they start firing regularly with one spike per tremor beat. With increasing force they show occasional double discharges which become continuously more frequent during still stronger efforts.

The intervals between the double discharges ranged between 20 and 70 ms. A typical record is shown in Fig. 4. The transition from the grouped

FIG. 6. Frequency profile, interval and joint interval histograms calculated for a single muscle fibre, recorded from the first dorsal interosseous muscle of a patient with Parkinsonian tremor during stationary isometric contraction of 200 g.

discharges to periods of more or less regular discharges is always accompanied by a decrease in tremor amplitude and by an increase in the firing frequency of the unit. During regular discharge periods the tremor sometimes disappears completely.

The characteristic changes of the discharge properties of smaller motoneurons in patients with Parkinsonism tremor become apparent if displayed by the frequency profile and the interval histograms. In normal subjects the frequency profile (Fig. 5a) of a single fibre recorded during steady isometric contraction (Fig. 5b) is characterized by a regular discharge. The non-sequential interval histogram (Fig. 5c) and the joint interval histogram (Fig. 5d) show a normal distribution without serial dependencies so that interval length varies randomly around a mean value. In addition, the serial and autocorrelation function show no relevant dependencies along a sequence of intervals so that these results, which are typical for normal subjects imply that the underlying spike generating process resembles a stochastic point process.

Figure 6 shows that the discharge and interval pattern of small units is basically changed in patients with Parkinsonism tremor. The frequency profile is irregular, the interval histogram is bi- or multimodal and the joint interval histogram shows a typical pattern with three different groups. Since each point in the joint interval histogram represents the length of two adjacent intervals, group 1 consists of intervals of approximately equal length so that the points have about the same distance from the ordinate and from the abscissa (see also legend). Group 1 corresponds to the periods of regular discharges as illustrated at the right end of Fig. 4. Groups 2 and 3 represent the typical short-long and long-short interval sequences during double discharges. This rhythmicity can additionally be shown by the autocorrelation function.

Tremor amplitude is shown to decrease rapidly with increasing isometric tension in Fig. 1. Figure 7 shows the corresponding change of the impulse rate profile and, in particular, the joint interval histogram (JIH). In Fig. 7a, the patient was asked to hold force constant at 200 g, in Fig. 7b at 300 g and in Fig. 7c at 350 g. The corresponding histograms show that with increasing force the frequency profile becomes

FIG. 7. Frequency profiles and joint interval histograms of a unit recorded from the first dorsal interosseous muscle of a patient with Parkinson's disease and tremor during different strengths of isometric contractions: 200 g (a), 300 g (b), 350 g (c).

FIG. 8. Frequency profile and joint interval histogram of a single unit recorded from the long finger extensor of a tremor patient during stationary isometric contraction of 200 g.

FIG. 9. Multi-spike recording and tremor record from the first dorsal interosseous muscle of a patient with Parkinson's disease.

more regular and the three different groups in the JIH tend to fuse.

Figure 8 shows a typical record from *m. extensor digitorum longus*. In this muscle the discharge frequency is generally higher and, during tremor, triple discharges are sometimes seen instead of double discharges. These triple discharges show the two characteristic short-long and long-short intervals and in addition a small group of short-short intervals.

According to the results described for tremor frequency and amplitude, changes of muscle length by variation of hand position have virtually no influence on the discharge pattern of motor units from the long finger extensor muscle.

REGULAR FIRING In contrast with the smaller units the motor units with larger potentials showed no or rarely grouped discharges but fired regularly also during strong contractions or tremor beats. This inference is based on the correlation between firing pattern and recruitment. The earlier a unit is recruited, the higher is the probability of grouped firing. This is illustrated in Fig. 9 which shows a multi-unit recording by a low impedance electrode where one motor unit fires preferentially repetitively and two others regularly. During the tremor beats the unit with the smaller spike, which corresponds to the lowest threshold unit, always starts firing before the larger spike units. The temporal order of firing of the three units is in accordance with spike amplitude. That the spike amplitudes in this case really correspond to the recruitment order so that increasing spike amplitudes correspond to successively higher threshold units is shown by the correlation between firing and tremor amplitude. During periods with weaker tremor beats only one or

two units are active. If the tremor becomes stronger, the smallest spike unit discharges mostly repetitively, but the large spike units do not show double discharges. At weaker contractions, the unit with smallest spike also discharges only once per tremor beat.

The close correlation between recruitment of a motor unit and conduction velocity of its efferent nerve fibre and thus with the size of the motoneurone has been described elsewhere (Freund *et al.*, 1972).

DISCUSSION

Grouped discharges of many motor units are the neuronal mechanism of tremor. In Parkinson's disease, most authors have regarded tremor during muscular activity as a manifestation of the resting tremor mechanism. In contrast, De Jong (1926) and in particular Lance *et al.* (1963) distinguished an action tremor from resting tremor on the basis of different characteristics observed in the two tremor forms. One of the main differences was the fact that resting tremor showed frequencies between 3.1–6.4/s and action tremor between 7 and 12/s. Lance *et al.* (1963) found no instance in which a gradual change in the frequency of resting tremor transmuted itself into a characteristic action tremor. Usually the resting tremor ceased before the faster action tremor started. In contrast, Bishop *et al.* (1948) observed that the frequency of Parkinsonism tremor may double during activity.

Our own tremor records have shown consistently that action tremor is not a constant faster rhythm, but that its frequency depends on the strength of isometric contraction of the muscle. This seems reasonable on the basis of the relationship between tremor and discharge

rate of the motoneurone. This relationship is commonly 1:1 for the larger and 1:2 for the smaller motor units (Fig. 9), since a particular unit discharges either once, twice, or both alternatively at each tremor beat. The increase of discharge rate with increasing force is well established and therefore corresponds to the increase in tremor frequency as long as the ratio between tremor and discharge rate remains constant.

From common observation and by the results of frequency analysis of finger and hand tremor (Halliday and Redfearn, 1956; Sutton and Sykes, 1967), it is well known that physiological tremor frequencies peak in the range between 8–12/s. One of the main differences between physiological and Parkinsonian tremor is that the latter has about half the frequency of the former. The comparison between resting and action tremor as well as between different action tremors has, however, always to refer to the force of contraction. With increasing isometric contractions tremor becomes considerably faster. The decline of tremor amplitude with increasing tremor rate continues without any enhancement into the frequency domain of physiological tremor at rest or weak contractions. There is no additional 'servo-loop oscillation' adding to the tremor of Parkinsonism if the frequency enters the 8–12/s range.

The *amplitude* of the tremor of Parkinsonism is considerably larger than that of physiological tremor. This can at least partially be explained by the different summation of the more or less fused contractions of single motor units at different discharge frequencies in the two tremor forms. At weak contractions the small units and at stronger contractions the larger units discharge only once per tremor beat. This implies that in these cases the firing rate of motoneurons in Parkinson's disease is considerably lower than in normal subjects (Fig. 3). In Parkinson's disease the motor units become recruited at frequencies between 3 and 5/s and in normal subjects between 7–9/s. At these low discharge rates the muscle fibres produce pure twitch contractions without any fusion. This can be calculated on the basis of the measurement of contraction time of single motor units in man in the methods described by Buchthal and Schmalbruch (1970) or by Milner-Brown *et al.* (1973a). The total con-

traction time of a single twitch contraction in the first dorsal interosseous muscle varies between 120 and 200 ms for units of different size (own measurements, unpublished). The lower frequency limit below which single twitches do not fuse at all is therefore 5–8/s. Milner-Brown *et al.* (1973a) obtained still lower values. They calculated the gain of single human motor units by measuring the change in gram for each impulse/second modulation in discharge rate of the unit at frequencies between 0.3 and 30/s. The gain decreased rapidly if frequency exceeded firing rates of 3–4/s. This will be a powerful mechanism determining tremor amplitude. The summation of unfused twitch contractions during synchronous activity of many motoneurons obviously achieves higher amplitudes than of partially fused twitches during higher firing rates. This explains a part of the amplitude differences between the tremor of Parkinsonism and physiological tremor and, further, the decrease of tremor amplitude with increasing firing rates during increasing force.

Another reason for the larger amplitudes of Parkinsonism tremor as compared with physiological tremor forms are the double or sometimes triple discharges of the smaller units during the tremor beats. The latter mechanism enhances tremor, since the two or three contractions corresponding to the repetitive discharges summate by partial fusion but then, during the subsequent long interval, decline to zero. Although double discharges occur also in other diseases (for reference, see Das Gupta, 1963) they were not or only exceptionally observed in physiological tremor (Jung, 1941; Taylor, 1962). Our recordings from patients with Parkinson's disease showed that double discharges are a common feature of the smaller low threshold units if the strength of contraction exceeds a certain level. The intervals between these double discharges are 20–70 ms. The same values were found by Das Gupta (1963) and Renou *et al.* (1970). The most characteristic feature of the tremor of Parkinsonism is the long interval following these double discharges. Whereas the double discharges and the coactivation of other units indicate a period of increased excitability, probably due to rebound excitation after inhibition, the pause between these bursts suggests a period of inhibition. This inhibition is probably

the mechanism underlying the characteristic low firing rates of motoneurons in Parkinson's disease, which is also observed in patients with akinetic forms of this disease without tremor. The motoneuronal frequency modulation is between 4 and 10/s as compared with 8–20/s in the first dorsal interosseous muscle of normal subjects. This low frequency may be one reason for the slight weakness in Parkinson's disease, since the increase in force by increasing firing rates is strongly limited so that the optimal tetanic fusion cannot be achieved. As mentioned above, higher discharge rates achieved by repetitive firing at one point in the tremor cycle cannot compensate for this since long intervals occur between the bursts.

The prolonged 'inhibition' between the spike bursts seems to be a basic functional disturbance. The reverse case, that strong rhythmic excitation with increased postexcitatory inhibition is the primary change, is less probable since the intervals between double or triple discharges are too long and discharge rates are generally too low. For the same reason an increased Renshaw inhibition has been rejected by Das Gupta (1963).

The assumption that the central lesion in Parkinson's disease with tremor produces a stronger and prolonged inhibition, no matter whether this is synaptically an inhibition or disfacilitation, explains two phenomena. (1) The experience that the tremor frequency and amplitude depend to some extent on segmental inputs. (2) The low discharge and tremor rates and their acceleration with increasing force. In both cases the duration of inhibition is modified by different strengths of excitatory and inhibitory inputs. In the case of stronger voluntary contractions the higher supraspinal excitatory drive obviously overcomes inhibition so that the longer intervals separating the bursts shorten. As a consequence, the discharge becomes more regular and tremor diminishes or disappears. This increasing firing rate during increasing isometric tension is a strong argument against the hypothesis of enhanced Golgi inhibition (Hufschmidt, 1962; Maxion, 1972; McLellan, 1973). In this case the burst interval should increase instead of decrease with raising isometric tensions.

The recruitment of the motor units according to size (Henneman, 1957) which applies also for voluntary innervation (Freund *et al.*, 1972;

Freund *et al.*, 1973; Milner-Brown *et al.*, 1973b) can also be observed during the tremor beats. Since tremor produces considerable changes of force, the smaller, lower threshold units are always recruited before the larger, higher threshold units. Confirmation that low and high threshold units correspond respectively to smaller and larger motoneurons has been made on the basis of conduction velocity measurements of the efferent nerve fibres (Freund *et al.*, 1972) and on the basis of the contractile properties of the motor units (Milner-Brown *et al.*, 1973a). The greater excitability of the earlier recruited units is also illustrated by their repetitive discharges which cannot or rarely be observed with the higher threshold units.

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