Parallel Neuronal Mechanisms Underlying Physiological Force Tremor in Steady Muscle Contractions of Humans

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Christakos, Constantinos N., Nikos A. Papadimitriou, and Sophia Erimaki. Parallel neuronal mechanisms underlying physiological force tremor in steady muscle contractions of humans. J Neurophysiol 95: 53–66, 2006. First published September 14, 2005; doi:10.1152/jn.00051.2005. We present results from a study of the 6- to 12-Hz force tremor in relation to motor unit (MU) firing synchrony. Our experimental observations from 32 subjects, 321 contractions, and 427 recorded MUs reveal that tremor is accompanied by corresponding, in-phase MU rhythms that are additional to the ones at the MU intrinsic firing rates. This rhythmic synchrony is widespread and has a uniform strength that ranges from near zero to very large (MU/MU coherence > 0.50) in different contractions. Both the synchrony and the tremor are suppressed during ischemia, and this strongly suggests an involvement of spindle feedback in their generation. Furthermore, in the presence of substantial synchrony, the tremor enhancement, relative to the minimal tremor of ischemia, reflects the strength of the synchrony. Theoretical considerations based on these observations indicate that the muscle force signal is expected to show 1) frequency components in the band of the firing rates of the last-recruited, large MUs, and 2) because of the synchronized MU rhythms, an additional, distinct component with a size reflecting the strength of synchrony. Furthermore, synchronized MU rhythms, with frequencies in the 6- to 12-Hz range, are expected to arise from self-oscillations in the monosynaptic stretch reflex loop, due primarily to the associated muscle delay (several tens of milliseconds). Our results therefore reveal the parallel action of two tremor mechanisms, one of which involves MU synchrony probably caused by loop action. Clearly, the results on the synchrony and its impact also apply to other possible generators of tremor synchrony, including supraspinal ones.

INTRODUCTION

The 6- to 12-Hz physiological force tremor is a ubiquitous characteristic of steady (constant-strength) muscle contractions and has been extensively studied in humans. However, its exact origin and neuronal mechanism remain uncertain (see Elble and Koller 1990; McAuley and Marsden 2000; Windhorst 1988). Such tremors in the mechanical activity of muscles are clearly a main source of the tremors of body segments. Therefore understanding the neuronal mechanism of force tremor is also important because it may facilitate the study of a wide variety of limb tremors, including enhanced physiological and different pathological ones.

In various previous studies, strong evidence has been presented in support of either of the two major hypotheses on the neuronal mechanism of force tremor. These are 1) the physiological mechanical activity of the last-recruited motor units (MUs) that fire within a narrow frequency band in an uncorrelated fashion or with weak correlations (Allum et al. 1978; Christakos 1982c), and 2) action in the monosynaptic stretch reflex loop, which synchronizes MU firing at a frequency corresponding to the delay of signal transmission around the loop (Hagbarth and Young 1979; Lippold 1970). These two hypotheses have generally been treated as mutually exclusive. Also, various objections have been raised against each one of them. Consequently, the issue remains unsettled.

In addition, there exist hypotheses implicating other central tremor generators. These include spinal tremor sources, such as the Renshaw cell system in the hypothesis of Elble and Randall (1976), who were the first to show coherent MU tremor rhythms; and supraspinal sources, like the inferior olive (Llinas and Yarom 1986), where 4- to 6-Hz subthreshold oscillations were observed and were enhanced by harmaline (a drug with tremorogenic properties), and the cortex, or possibly subcortical structures, where neural rhythmicities coherent with tremor have recently been observed (e.g., McAuley and Marsden 2000; Raethjen et al. 2002).

Any such generator is, however, expected to interact with the alpha-motoneuron/muscle-spindle system in regard to the tremor synchrony and properties. Therefore the resolution of the above issue, and in particular the specification of the role of the monosynaptic reflex loop with respect to MU synchrony and tremor properties, can also provide a useful basis for the study of other possible tremor generators.

It should be noted that systematic studies of the tremor synchrony of MUs are uncommon, mainly because of the experimental and computational difficulties of unit-to-unit (UTU) analysis when studying population synchrony. In a recent such study, Halliday et al. (1999), using coherence analysis between MU pairs and acceleration tremor, showed the presence of synchrony in the range of 1–12 Hz and a corresponding contribution to tremor. MU coherences in the range of 1–12 Hz were also a consistent feature in the experiments of Farmer et al. (1993), whereas increased MU synchronization (0 lag), quantified by time-domain analysis, was observed by Logigian et al. (1988) in cases of large-amplitude tremors.

In a previous human study of MU firing synchrony during contractions of the first dorsal interrosseus (FDI) muscle of the hand (Erimaki and Christakos 1999), we used a novel and
efficient technique for analysis of population synchrony, namely unit-to-aggregate coherence and correlation computations (Christakos 1997; Christakos and Giatroudaki 1998b). Certain principles of this technique were previously used by us in collaborative studies of respiratory and neuromuscular mechanisms (Christakos et al. 1994; Iyer et al. 1994).

In the 1999 study, we described two types of force-tremor, defined on the basis of tremor properties and neuronal substrate: I) small-amplitude and fairly irregular tremor, without, or with a limited, rhythmical MU synchrony, and II) large and nearly single-frequency tremor, accompanied by a widespread and moderate-to-strong rhythmical MU synchrony. Moreover, in preliminary experiments using ischemia, we observed that the probable block of Ia feedback practically eliminated the strong synchrony that accompanies the type II tremor and changed the tremor to type I. We therefore proposed that the above two mechanisms, namely MU firing rhythmicity and stretch reflex oscillations, are responsible for two different tremor types.

In this study, we pursued the analysis of force tremor mechanisms in the same human muscle (FDI) and examined large numbers of subjects, contractions, and recorded MUs. We performed systematic analyses of MU firing synchrony, using the same efficient technique, to describe the neuronal substrate of this tremor; we used ischemia as a means of examining the possible role of the monosynaptic stretch reflex loop in the generation of the tremor synchrony of MUs; we also employed theoretical considerations to specify the mechanisms underlying tremor and assess their relative contributions to it.

Our results indicate that the large MU mechanism, which is the basis of type I tremor, acts in parallel with a second mechanism that causes a widespread and rhythmical MU firing synchrony. This second mechanism is primarily responsible for type II tremor and very probably involves spindles Ia feedback and loop oscillations. In any given contraction, the strength of the MU synchrony determines the relative contributions of the two mechanisms and their impact on the properties of the resulting tremor. Thus there are contractions where either mechanism dominates, but more often, both of them significantly contribute to tremor.

Preliminary reports have been presented in abstract form (Christakos and Erimaki 2000; Papadimitriou et al. 2003).

METHODS

Experiments and data acquisition

The experiments were conducted on 32 neurologically normal volunteers (age, 20–48 years), who gave informed consent. Approval for this study was obtained from the Ethics Committee of our Medical School.

In the recording sessions, the subjects assumed a comfortable sitting position, and their dominant hand and arm were secured on the lab bench, in front of the force transducer (WPI Fort1000). The subjects exerted abduction force on a vertical plane with the lateral side of the horizontally extended index finger and were instructed to keep the nearly isometric force of the FDI muscle of the hand (prime agonist) at a constant level.

Simultaneous 2-min records were obtained of the force (using the force transducer), the surface EMG (using Ag–AgCl disk electrodes), and intramuscular EMG (using bifilar nichrome wire electrodes, 40 μm). The data were digitized (sampling rate of 5 kHz) and stored using the program LabView.

Discrimination of single MU spike trains in the intramuscular electrical activity was performed by a combination of a threshold operation, a template-matching algorithm, and manual sorting. This provided usually one and sometimes two to four MUs per recording. Spike trains were represented as sequences of 0s and 1s. All recorded signals, including the discrete sequences, were low-pass filtered at 250 Hz and resampled at 500 Hz for analysis (Christakos et al. 1984). The filtering was digital and introduced no time shifts.

Ischemia

This manipulation was used to examine the possible involvement of the monosynaptic stretch reflex loop in the generation of tremor and the accompanying MU synchrony. There is evidence from various studies, including H-reflex ones, that such short-term arterial occlusion blocks the feedback of Ia afferents from primary muscle spindle endings through a selective action on these large fibers (e.g., Cresswell and Loscher 2000; Fellows et al. 1993; Hayashi et al. 1987; Lippold 1970; Schmitzler et al. 1997; Sinkjaer et al. 2000). Therefore this procedure is equivalent to interrupting the monosynaptic reflex loop. In principle, other loops comprising large afferent fibers could also be interrupted.

A sphygmonanometer cuff applied to the upper arm was inflated to 200 mmHg and kept for a total of about 12 min. The recordings started after about 10 min of ischemia to ensure a nearly complete block of Ia afferents (Schmitzler et al. 1997) and lasted 2 more min.

Data analysis

Analyses were performed in both the frequency- and the time-domain using MATLAB (MathWorks, Natick, MA). Frequency-domain analysis, using the fast Fourier transform, was performed on pairs of recorded activities in the standard way (Rosenberg et al. 1989; Wang et al. 2004). It included J) segmentation of the 2-min time-series in 60, 2-s-long segments, together with mean removal and windowing (Hanning) for each data segment; 2) computation of the auto-spectra and the cross-spectrum (periodograms) from each segment, and J) final estimation of the auto-spectra and the cross-spectrum of the activity pair by averaging the estimates from the individual segments. The coherence spectrum was estimated as the squared modulus of the cross-spectrum divided by the product of the individual auto-spectra.

The time-domain analysis included computation of interspike interval (ISI) histograms of MU spike trains and cross-correlograms of pairs of activities.

ANALYSIS OF SYNCHRONY

In the study of rhythmical MU synchrony, we used a combination of unit-to-aggregate (UTA) coherence and cross-correlation analysis, where in this case, the unitary signal is MU activity and the aggregate signal is the muscle force waveform. According to mathematical and simulation studies (Christakos 1994, 1997; Christakos and Giatroudaki 1998a,b), this method provides an experimentally and computationally efficient means of detection of population synchrony and estimation of its parameters. These are 1) the extent of synchrony, which is defined as the proportion of the correlated units within the population, and thus ranges from 0 to 100%; 2) the strength of the units’ correlations, or, equivalently, the unit-to-unit (UTU) coherence; and 3) the phases of the correlated units, θi, which are properly described in terms of units’ delays, di, relative to the aggregate activity (common reference signal), as p = ωd, where ω is the frequency of synchrony (Christakos et al. 1984).

Specifically, coherence computations on a sample of pairs of simultaneously recorded unit/population activities 1) enable the detection of population synchrony, through even a single observation of a nonzero UTA coherence in the sample; 2) provide an estimate of the extent of synchrony, as the fraction of nonzero UTA coherences in the sample; and 3) furnish information on the strength of synchrony and
its distribution within the population. Moreover, 4) UTA cross-correlation computations for the coherent units in the sample yield an estimate of the phase distribution in the form of a histogram of units’ delays relative to the aggregate activity.

These additional time-domain computations are recommended, because phase information at each frequency of synchrony can only be reliably obtained from the UTA cross-spectrum when the estimated UTA coherence is near 1, and the variance of the estimate is small, as determined by the equivalent number of degrees of freedom. Otherwise, the linearity assumption for such input/output relations is not valid.

Clearly, for a low UTA coherence, the variance of the UTA cross-correlation estimator will also be large, thus affecting the estimation of the delay. However, the general form of the cross-correlogram, which in the present spike/force analysis represents a spike-triggered average, can at least provide a rough estimate of the time relation between the unitary and the aggregate signal.

In regard to the estimation of the strength of the MU tremor synchrony, because this synchrony was found (RESULTS) to be both widespread and uniform, with the MU tremor rhythms in-phase, the value of the UTU coherence is very close to the square of that of the UTA coherence (Christakos 1997). This property enables the estimation of the strength of population synchrony in terms of UTU coherence estimates obtained from respective UTA coherence estimates.

It should be noted that, in the presence of strong recording noise in the frequency-band of synchrony, squaring the underestimated UTA coherence will lead to an even greater underestimation of the UTA coherence; therefore this rule has to be used with caution. However, in our study, the square rule was verified in all contractions with pairs of simultaneously recorded MUs, even though some noise was always present. Therefore when the noise appears unusually strong, the UTA analysis could be combined, if possible, with a limited UTU analysis on some pairs of simultaneous units for control.

For all contractions where the MU/force coherences were not statistically significant, we used additional computations of coherence between the rectified EMG and the muscle force signal, i.e., an aggregate-to-aggregate (ATA) coherence, for detection of synchrony.

According to the above studies (Christakos 1997; Christakos and Giatroudaki 1998a), because of the in-phase and widespread nature of the MU tremor synchrony, the ATA coherence function between the EMG and the muscle force or associated kinematic variables (e.g., movement acceleration) is very sensitive in reflecting the strength of synchrony. It is therefore a very useful tool for easy detection of such synchrony, determination of the frequency of synchrony and, possibly, characterization of activity states.

It is important to stress, however, that because of the high sensitivity of the ATA coherence in such situations, this function has large values even if the synchrony is very weak; in addition, it shows strong saturation effects (Christakos 1997). In Fig. 2, where the MU/force coherence is barely detectable (<0.10) and therefore the corresponding MU/MU coherence is <0.01, the 0.70 EMG/force coherence certainly gives the misleading impression of a strong MU synchrony. Apart from the overestimation of the strength, the saturation effects exhibited by this function are also expected to complicate comparisons of synchrony in different conditions.

Given the in-phase tremor rhythms for all MUs, such overestimation and saturation effects are also expected for the EMG/EEG (or the EMG/MEG) coherence, in cases where coherent tremor rhythms dominate the recorded cortical population activity. It should be noted, however, that in situations where the particular activity is dominated by additional cortical rhythms at, or around, the tremor frequency, which are not coherent with tremor, low values are expected for this ATA coherence (Christakos 1997; Christakos et al. 2003). Such low values may represent an underestimation of the true coherence between the units of the two populations.

For the above reasons, ATA coherence analysis could only be used with great caution for estimation of the strength of population synchrony in the case of tremor.

Finally, for the 60 segments used in the spectral analyses of this study and for the smooth data tapering that was used for leakage suppression, the threshold for a significant coherence at the 99% confidence level is ~0.08 (Rosenberg et al. 1989; Wang et al. 2004). Therefore in cases where the MU/force coherence was below this threshold, while the EMG/force coherence was significant, the synchrony was considered minimal and, for the purposes of this study, practically absent.

The justification for such decisions is provided by the above-described square relationship that holds for the units of this study between the UTA and the UTU coherence. Accordingly, even a marginally significant MU/force coherence (~0.08) implies a very low coherence (~0.0065) between MUs. Such a minimal synchrony has a very limited role in tremor formation (RESULTS).

TREMOR PARAMETERS. Two important parameters of the tremor oscillation are its amplitude and its regularity. The tremor amplitude was estimated as the square root of the total power in the frequency-band of the auto-spectral deflection representing the tremor. This value was subsequently presented as maximal voluntary contraction (%MVC).

As a measure of the tremor regularity, the ratio q of the peak power density in the tremor frequency-band to the total density within the particular band was used. This is the ratio of the auto-spectral component at the central tremor frequency to the sum of all components forming the tremor deflection and represents a measure of concentration of power around the central frequency of tremor. Its reciprocal corresponds to the effective tremor bandwidth, \( eBW = 1/q \), within which the total tremor power would be uniformly distributed.

For example, in the case of a nearly regular analog signal (approaching a sine wave), q is close to 1, and eBW is represented by one frequency bin. In the case of a perfectly irregular signal having uniform power density within a band covering n frequency bins, \( q = 1/n \), and \( eBF = \text{equals} n \) frequency bins. Hurtado et al. (2000) have used a similar method in studies of Parkinsonian tremor.

STATISTICAL ANALYSIS. All data were analyzed using nonparametric tests (SPSSv12.0 statistical package). Estimates of Spearman rank order correlation coefficient were used to examine possible relationships between such variables as MU firing rate, mean level of contraction, and MU/force coherence. To assess the effects of ischemia on the tremor parameters and MU synchrony, Friedman ANOVA by ranks was used for multiple within-subjects comparisons (preischemia, ischemia, and postischemia). All tests were performed at the \( P < 0.05 \) level.

RESULTS

Force tremor and its properties in relation to rhythmical MU firing synchrony

Force tremor was present in all 321 steady contractions of the 32 subjects of this study. The tremor was manifested as a local peak (or deflection) in the auto-spectrum of the muscle force signal. Its central frequency was in the range 6–11.6 Hz (mean, 8.6 ± 1.4 Hz) for the different contractions and subjects.

A wide range of force levels (1–74% MVC) was used in the subjects' contractions. The firing rates of the recorded MUs, including sometimes pairs, triplets, or quadruplets of simultaneous MUs, also covered a wide range of values (6–19 Hz). MU tremor synchrony was present in the different contractions of the subjects and ranged from barely detectable, but not
reliably measurable, to strong. In the former case, the synchrony was considered to be practically absent (METHODS).

Table 1 summarizes the conditions and observations for the total 321 contractions of our subjects.

**TREMOR IN THE PRACTICAL ABSENCE OF MU SYNCHRONY.** In 37 of the contractions (11 subjects), no tremor synchrony of MUs could be reliably measured by MU/force coherence analysis; however, in general, the presence of a minimal tremor synchrony was revealed by EMG/force coherence analysis (METHODS). The tremor in such situations tended to be small and irregular.

The time record in Fig. 1D shows a very small and fairly irregular tremor that is represented by a small local deflection between 8 and 12.5 Hz in the force auto-spectrum (Fig. 1A).

A simultaneously recorded motor unit (MU1) fires rhythmically at 11.5 Hz, i.e., within the band of the tremor frequencies, as is indicated by the corresponding large peak and subsequent harmonic peaks in the auto-spectrum of Fig. 1B and also by the respective, narrow ISI histogram (Fig. 1E). However, as can be seen in the time record, the spikes of MU1 occur randomly relative to the tremor oscillation. The same is indicated by the nearly zero MU1/force coherence within the tremor frequency-band (Fig. 1C) and also by the practically flat MU1/force cross-correlogram (Fig. 1F).

The nearly zero MU1/force coherence reflects limited, if any, correlations of MU1 to other active MUs (METHODS). Indeed, a second, simultaneous unit (MU2) that also fired rhythmically within the tremor band (at 12 Hz) shows zero coherence to both the tremor (Fig. 1G) and MU1 (Fig. 1H).

As in the case of the MUs of the above example, the estimated MU/force coherence was <0.08 for all 46 recorded MUs (including 7 pairs and 1 triplet of simultaneously recorded MUs) in the 37 contractions. This occurred whether the MUs fired within the tremor frequency band or not, and reveals a similar behavior of active MUs with respect to the synchrony.

The presence of a minimal tremor synchrony of MUs in the 37 contractions was, however, revealed by EMG/force coherence analysis. An example is depicted in Fig. 2. In this case, the

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**TABLE 1. Summary of conditions and experimental observations in the subjects' contractions**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No of contr</th>
<th>No of MUs</th>
<th>ContrLev, %MVC</th>
<th>MUFr, Hz</th>
<th>MU/FCoh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Tremor Synchrony (+)</td>
<td>Tremor Synchrony (-)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>32</td>
<td>11</td>
<td>1–74</td>
<td>16.8 (13.1)</td>
</tr>
<tr>
<td></td>
<td>284</td>
<td>284</td>
<td>37</td>
<td>1–74</td>
<td>16.9 (12.6)</td>
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<tr>
<td></td>
<td>427</td>
<td>381</td>
<td>46</td>
<td>1–51</td>
<td>16.5 (14.5)</td>
</tr>
<tr>
<td></td>
<td>64 p, 12 t, 3 q</td>
<td></td>
<td></td>
<td>6–19</td>
<td>10.7 (2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.5–19</td>
<td>6–19</td>
<td>10.6 (2.4)</td>
<td>12.1 (2.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08–0.09</td>
<td>&lt;0.08</td>
<td>0.34 (0.17)</td>
<td></td>
</tr>
</tbody>
</table>

Classification of our results, based on the presence or not of MU tremor synchrony. The symbols p, t, q denote simultaneously recorded MU pairs, triplets, or quadruplets, respectively. The contraction level is measured in percent of maximal voluntary contraction (%MVC), and the MU firing rate (MUFr) in Hz. For the number of segments used in our study, MU/force coherences (MU/FCoh) >0.08 are significant. MU, motor unit.

MU/force coherence function shows marginally significant peaks around 7 Hz (vertical dotted line) and its first harmonic, and it is practically flat, with values near zero, at higher frequencies. In contrast, the corresponding EMG/force coherence function shows a distinct peak of 0.70 around 7 Hz and has significant values up to 35 Hz. Importantly, 7 Hz was the frequency of the tremor synchrony seen in other contractions of the particular subject.

Although large, because of the high sensitivity of the EMG/force coherence function (METHODS), the 0.70 value in actuality represents a very weak MU synchrony (strength of the order of 0.08 in terms of MU/force coherence and only 0.0064 in terms of MU/MU coherence; METHODS). As described later, such a
minimal synchrony has a very limited influence on tremor and its properties.

TREMOR IN THE PRESENCE OF MU SYNCHRONY. In the remaining 284 contractions (32 subjects), the force tremor was accompanied by significant MU/force coherences within the tremor frequency band. The strength of the MU synchrony varied among subjects and contractions, and the tremor tended to be large and regular when this strength was large.

The time record in Fig. 3D shows a fairly small and irregular tremor that is represented by the small peak around 8.5 Hz in the force auto-spectrum of Fig. 3A (vertical dotted line).

In this case, two simultaneously recorded MU activities show measurable coherences to the force tremor around 8.5 Hz (dotted line), even though MU1 fires at 10.5 Hz (Fig. 3B) and MU2 at 11.5 Hz (auto-spectrum not shown). The respective values are very similar, 0.20 and 0.18 (Fig. 3C and G); they reflect the presence of weak correlations between rhythms at 8.5 Hz in the activities of the two MUs, as well as other active MUs (METHODS). The corresponding coherence between the two MUs has a nonsignificant value of the order of 0.04 (Fig. 3H), which is very close to the squares of the coherences of the individual MUs to tremor (METHODS).

In the time-domain, the above MU/force coherences at 8.5 Hz reflect a tendency for some of the spikes of the two MUs to occur rhythmically near the local minima of the tremor oscillation (e.g., time record of MU1 in Fig. 3D). This was verified by the respective MU/force correlograms, which showed a decaying oscillation with a central trough at zero lag (e.g., Fig. 3F for MU1). Because such correlograms represent spike-triggered averages, the locking of some MU spikes to tremor minima becomes clear.

The time record in Fig. 4D, for a contraction of the same subject (EK) as in Fig. 1, shows a force tremor that is large in amplitude and nearly regular. This tremor is manifested as a large and sharp peak at 8 Hz in the force auto-spectrum of Fig. 4A (vertical dotted line).

For the simultaneously recorded MU1 shown in this figure, the dual peak in its auto-spectrum (Fig. 4B), i.e., the small but distinct peak at 8 Hz and the large one at 11 Hz, reveals a complex firing pattern of the unit with two rhythmic components. Of these components, the one at the tremor frequency is strongly correlated to the tremor oscillation, as is indicated by

FIG. 2. Comparison of MU/force and EMG/force coherence estimates (subject KL). Top: coherence of simultaneous muscle force signal and MU spike activity in a steady contraction showing a minimal MU synchrony around 7 Hz. Note the marginally significant coherence peaks at 7 Hz (vertical dotted line) and its 1st harmonic. Bottom: coherence between EMG and force in the same contraction. Note the high coherence up to 35 Hz, and, in particular, the large peaks around 7 and 14 Hz, which give a highly overrated picture of the true MU synchrony.
the corresponding sharp and large (0.74) peak in the MU1/force coherence spectrum (Fig. 4C). In addition, the time record in Fig. 4D again reveals a tendency for some of the MU spikes to occur rhythmically near the minima of the tremor oscillation. The same is indicated by the central trough at zero lag in the oscillatory MU/force cross-correlogram in Fig. 4F.

The high MU1/force coherence reflects strong correlations between rhythms at 8 Hz in the firing of this and other active MUs (METHODS). Indeed, a second, simultaneously recorded unit (MU2) firing rhythmically at 8 Hz shows high coherences at 8 Hz to both the force tremor (0.77; Fig. 4G) and MU1 (0.58; Fig. 4H). It should be noted that the coherences to the force of MU1 and MU2 are again very similar, and both are close to the square root of the MU1/MU2 coherence. It should also be stressed that the spikes of MU2 (data not shown), in a one-to-one relation to the tremor cycles, exhibited a clear tendency to occur rhythmically near the minima of the tremor oscillation, i.e., the tremor rhythms of the two recorded MUs were in phase.

As in the cases of the MUs of Figs. 3 and 4, the estimated MU/tremor coherence was $\geq 0.08$ for all 381 recorded MUs in the 284 contractions, including 64 pairs, 12 triplets, and 3 quadruplets of simultaneously recorded MUs. This occurred whether the MUs fired within the tremor frequency band or not. The range of these coherences was 0.08–0.90 (mean, 0.34 ± 0.17).

As described in METHODS, such coherence values reflect all three parameters of the MU tremor synchrony. Additional analyses and considerations regarding these parameters are presented below.

**CHARACTERISTICS OF THE TREMOR SYNCHRONY OF MUs.** Because all analyzed MUs in the 284 contractions showed significant tremor coherences, it can be concluded that the tremor synchrony of MUs was widespread.

Importantly, for the pairs, triplets, and quadruplets of simultaneously recorded MUs in certain contractions, the coherences of the units to tremor had similar values (usually within 10% and at most within 20% of each other; see Figs. 3 and 4). The differences between coherences in such MU pairs showed a statistically significant, negative relationship to the corresponding differences of firing rates (Spearman rank correlation coefficient, $-0.230; 0.01 < P < 0.05; n = 118$). However, the scatter diagram that was constructed from these MU pairs did not show any obvious trend, and linear regression analysis failed to reveal a significant relationship between such differences: $\text{DiffCoh} = 0.022 - 0.011\text{DiffFR} (r^2 = 0.027, P > 0.1)$.

On the basis of the above, it can be concluded that the tremor synchrony of MUs in the studied contractions had a fairly uniform strength within the population of active MUs.

For each MU, the coherence to tremor reflected a tendency for some MU spikes to occur rhythmically near the tremor minima, and this tendency ranged from weak to strong. Thus the tremor components of the firing of the different MUs were in-phase.

Specifically, the minimal observed MU firing rates were equal to the frequencies of the tremor synchrony for the different subjects. The spikes of such last-recruited MUs showed a tendency to occur rhythmically at the tremor minima. The firing patterns of MUs that fired above the frequency of synchrony were more complex. Thus when the firing rates of the MUs were much higher than the frequency of synchrony, the patterns usually consisted of rhythmic spikes near the tremor minima and additional, interspersed spikes, or they sometimes had rhythmic couplets of spikes around the tremor minima (also see Elble and Randall 1976; Logigian et al. 1988). On the other hand, for MU rates that did not exceed the frequency of synchrony by much, the patterns combined the intrinsic MU firing rhythm and the tremor rhythm (Fig. 4).

Therefore for the observed widespread, uniform-strength and in-phase tremor synchrony, its strength in the different contractions can be estimated in terms of MU/MU coherences by squaring the estimates of the respective MU/force coherences (METHODS). Thus the MU/MU coherences are found to be in the range 0.0064–0.81, i.e., the strength of the synchrony ranged from very small to very large.

It is important to note that experimental verification for certain of the very large MU/MU coherences, as estimated
from our sample of MU/force coherences, was possible because the particular contractions had simultaneous recordings of two or three MUs. For example, in the case of the maximal MU/force coherence (0.90) in our sample, a second, simultaneous MU showed a 0.89 coherence to the force, whereas the measured coherence between the two MUs was 0.83, i.e., very close to the squares of the individual MU/force coherences. As expected, in all cases of very strong synchrony, the tremor had very large amplitudes, and in this example, the tremor amplitude was of the order of 15% of the mean force.

Finally, we were not able to establish a relationship between MU/tremor coherence and muscle force level in our sample of 284 contractions (Spearman rank correlation coefficient, \( \rho = 0.065; P > 0.25; n = 284 \)). Importantly, the Spearman test also failed to reveal a significant relationship \( (P > 0.25) \) when performed within each of our subjects who had \( \geq 20 \) contractions.

**EFFECTS OF ISCHEMIA ON TREMOR AND ITS SYNCHRONY: PROBABLE INVOLVEMENT OF I\( \alpha \) AFFERENT FEEDBACK IN TREMOR GENERATION.**

According to the above observations, force tremor is accompanied by corresponding in-phase firing rhythms of MUs. To examine the possible involvement of the monosynaptic stretch reflex loop in the generation of such tremor-related MU rhythms and synchrony (see preliminary observations by Ermiaki and Christakos 1999), we used ischemia as a means of blocking the spindle (I\( \alpha \)) feedback (METHODS) during 23 steady contractions of 16 of our subjects.

In all tests, the clear effect of ischemia was the suppression, even close to elimination, of the rhythmical MU firing synchrony. This was accompanied by a reduction of the amplitude and regularity of tremor. Furthermore, removal of the occlusion reinstated the initial tremor and the synchronized MU rhythms. The example in Fig. 5 depicts the effects of ischemia for a contraction that initially showed large and regular tremor at 6.5 Hz (left column, vertical dotted line) accompanied by an MU/force coherence of 0.59, whereas the MU had its intrinsic firing at 9 Hz. As seen in the middle column, the application of the pressure did not change the MU firing rate, but it drastically reduced the 6.5 Hz component of the MU/force coherence (remaining coherence of \( \sim 0.10 \)). It also resulted in the appearance of a small and irregular tremor (inset: local deflection in the force auto-spectrum between 6.5 and 10 Hz). Finally, removal of the occlusion led to a situation similar to that before ischemia (right column).

Table 2 summarizes the conditions and effects for the ischemia tests. Clearly, the contraction level was practically constant in the three phases of each test, and the same applies to the firing rates of the MUs. However, during ischemia, the synchrony was much weaker, or practically absent, and the amplitude and regularity of the tremor were much smaller. Furthermore, the central frequency of tremor was slightly but consistently higher compared with that in the preischemia phase. Finally, the return to the initial values in the postsiscemia phase indicates that the effects of ischemia were transient.

These observations strongly suggest that I\( \alpha \) afferent feedback is greatly involved in the generation of the rhythmical MU tremor synchrony and the determination of the properties of the associated tremor component.

**IMPACT OF THE SYNCHRONY OF MUS ON THE TREMOR AMPLITUDE.**

In the preceding experiments, tremor was present during ischemia, even in the practical absence of MU synchrony. Such tremor is indeed expected, as the inevitable effect of the intrinsic firing rhythms of the last-recruited, large MUs (Christakos 1982c); it represents the minimal tremor at any contraction level, because the tremor of the MU synchrony can, in a first approximation, be considered additional to it (Christakos 1986).

We therefore compared the tremor amplitude before and during ischemia to obtain an estimate of the impact of the synchrony on this amplitude. To ensure that the contribution of the large MUs to the tremor dominated during ischemia, we
only considered cases where the MU/force coherence was not significant and the EMG/force coherence was low (cases of minimal MU synchrony).

Figure 6 depicts the relative tremor contribution of the synchronized MU rhythms in 15 such tests (12 subjects) as a function of the MU/force coherence. This contribution was obtained by subtracting the amplitude of the tremor of the large MUs, during ischemia from the total tremor amplitude in the preischemia phase, where MU synchrony was present, and normalizing the difference by the total tremor amplitude. The scatter diagram of Fig. 6 reveals a clear tendency for this ratio to increase as the strength of synchrony increases, with values ranging from ~0.2 to 0.9. Thus the impact of synchrony on tremor ranged from limited to dominant in the 15 contractions.

It is worth noting that for MU/force coherences that are within 1 SD (0.17) from the average coherence (0.34) in our sample of 381 MUs, the particular ratio in Fig. 6 ranges from ~0.3 to 0.7. This implies that in most of the contractions of our study, the tremor contribution of the synchrony ranged from about one-half to twice the contribution of the large MUs.

### Theoretical considerations

The above-described properties of the MU tremor synchrony, combined with data on the MUs of the FDI muscle, are used to model the frequency content of the muscle force waveform. In addition, the signal transmission around the monosynaptic stretch reflex loop is considered in order to specify the possible role of this loop in the generation of synchronized MU tremor rhythms. The latter analysis is directed by the widely used assumption that only conduction delays are involved in the particular signal transmission.

**FREQUENCY CONTENT OF THE MUSCLE FORCE WAVEFORM IN STEADY CONTRACTIONS.** The force outputs of the active MUs are customarily modeled as random signals, $x_i(t)$, which by superposition form the muscle force waveform, $x(t) = \Sigma_i x_i(t)$. Therefore the auto-spectrum of the muscle force signal equals the sum of all auto- and cross-spectra of the MU signals and can be written as (Christakos 1986)

$$S_x(\omega) = \Sigma_i S_i(\omega) + \Sigma_{i \neq k} \Re[S_i(\omega)S_k(\omega^*)]$$

where $S_i(\omega)$ are the auto-spectra of all $x_i$ and $\Re[S_i(\omega)]$ is the real part of the cross-spectra of all pairs of $x_i$.

During steady muscle contractions, the rhythmical discharge of each MU is reflected in a dominant component in the force auto-spectrum of the MU (Christakos 1982a). Moreover, for MUs that have coherent components of their firing at the tremor frequency, there exist additional auto- and cross-spectral components of their force signals at that frequency (e.g., the dual auto-spectral peak in Fig. 4B). Corresponding components also exist in the force outputs of the MUs (Christakos 1982a).

In light of our observations, the following hold for the terms in Eq. 1. 1) The cross-spectral components of the MUs are numerous, because the tremor synchrony is widespread. Specifically, for the FDI muscle, $n$ in Eq. 1 ranges from >50 in weak contractions to 150–200 in strong contractions (Christakos 1982c). Therefore the number of cross-spectral terms, which is given as $n^2 - n$, ranges from a few thousands to a few tens of thousands, i.e., it is much larger than that of the auto-spectral terms. 2) The particular components (real parts) have a positive sign, because the MU rhythms are in-phase, and are therefore simply superimposed in Eq. 1. 3) Because of the uniform strength of the tremor synchrony, the sizes of all such components increase in parallel as this strength increases, and range from near zero to large, i.e., comparable with those of the corresponding auto-spectral components (Christakos 1990; Weytjens and van Steenhage 1984).

As a consequence of the above, the auto-spectrum of the muscle force waveform is expected to show 1) in every contraction, components within a frequency-band, above, but next to the MU recruitment rate, where the last-recruited, large MUs fire (Christakos 1982c), and 2) in contractions showing MU synchrony, an additional component at the frequency of the synchrony, which is mainly caused by the numerous cross-spectral components of all MUs. The latter component is mixed with the components of the large MUs, and for moderate to strong synchrony, it prevails or dominates. According to the data of Fig. 6, this occurs for MU/force coherences above ~0.30 or MU/MU coherences >0.10.

### Table 2. Effects of ischemia on tremor parameters and MU synchrony

<table>
<thead>
<tr>
<th>$n = 23$</th>
<th>Preischemia</th>
<th>Ischemia</th>
<th>Postischemia</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ContrLev</td>
<td>13 ± 5.9</td>
<td>12.8 ± 5.8</td>
<td>12.9 ± 6.0</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>MUFr</td>
<td>10.5 ± 2.4</td>
<td>10.8 ± 2.5</td>
<td>10.7 ± 2.4</td>
<td>&gt;0.95</td>
</tr>
<tr>
<td>MU/FCoh</td>
<td>0.46 ± 0.18</td>
<td>0.12 ± 0.09</td>
<td>0.44 ± 0.18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ampl</td>
<td>1.9 ± 0.07</td>
<td>0.69 ± 0.4</td>
<td>2.12 ± 0.92</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eBW</td>
<td>2.89 ± 1.14</td>
<td>4.71 ± 2.03</td>
<td>2.97 ± 0.95</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CentrFreq</td>
<td>7.5 ± 1.04</td>
<td>9.2 ± 0.92</td>
<td>7.8 ± 1.25</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Values are ± SD. Conditions of the ischemia test with regard to contraction level (ContrLev, % MVC) and MU firing rate (MUFr, Hz); and effects of ischemia on MU/Force coherence (MU/FCoh), tremor amplitude (Ampl, % of ContrLev), effective bandwidth (eBW, Hz), and central frequency (CentrFreq, Hz). Friedman analysis of variance by ranks for multiple within subjects comparison was used for statistical evaluation. *P-values <0.05 indicate statistically significant effects (lower four rows). MU, motor unit; $n = 23$ contractions.
SPECIFICATION OF THE POSSIBLE ROLE OF THE MONOSYNAPTIC REFLEX LOOP IN TREMOR GENERATION. A self-oscillation representing tremor can occur in this closed-loop system because of signal transmission delays and has a period equal to the delay around the loop, so that the effects of the Ia feedback add to the ongoing tremor.

Specifically, in the case of force tremor, grouped spindle discharges occur in the decaying phase of each tremor cycle (phase of muscle lengthening; e.g., Hagbarth and Young 1979). Because of the practically simultaneous influence of Ia afferent activity on homonymous alpha-motoneurons (MNs) (Matthews 1981), there is a tendency for MNs to discharge in-phase. Each such group of MN discharges causes a muscle twitch which forms the subsequent tremor cycle, and this process repeats itself.

According to the schematic diagram of Fig. 7, the period of the rhythmical MU synchrony is the sum of 1) the muscle delay, from the initiation of each muscle twitch, which corresponds to a tremor minimum, to the point of the grouped spindle discharges, and 2) the afferent and efferent conduction delay, plus synaptic delays, until the initiation of the subsequent muscle twitch, i.e., the next tremor minimum.

The grouped spindle discharges occur near the point (Fig. 7) where the velocity of the length increase is maximal (Binder and Stuart 1980; Hagbarth and Young 1979; Lippold et al. 1957). Therefore the muscle delay for the FDI is of the order of several tens of milliseconds, according to experimental (Milner-Brown et al. 1973) and simulation (Christakos 1982c) studies. Its length reflects the fact that the decaying phase of the muscle twitch is mainly determined by the numerous slow and small MUs that are active at all contraction levels. This delay is much longer than the conduction one, which is of the order of 25–30 ms (e.g., Nakajima et al. 1996). Clearly, the total delay is of the order of 100 ms and corresponds to the typical tremor frequencies.

DISCUSSION

The main results of this study are 1) the estimation of the parameters of the MU tremor synchrony and of the associated contribution to tremor from large numbers of subjects, contractions, and recorded MUs; 2) the observation of a suppression of tremor and its synchrony during ischemia, which strongly suggests an involvement of Ia afferent feedback in tremor generation; and 3) the model of two parallel neuronal mechanisms of tremor, namely intrinsic MN firing rhythmicity and rhythmical MU synchronization probably caused by spinal stretch reflex rhythmicity.

Overview and combination of experimental and theoretical results

The present measurement of the MU tremor synchrony has revealed that this synchrony is always present, widespread, and practically uniform, but its strength ranges from near zero to very large (MU/MU coherence up to 0.80) in different contractions; exhibited the occurrence of small and irregular tremor in contractions where the strength of synchrony is very small, including contractions during ischemia where the Ia afferent feedback is probably interrupted (also see Burne et al. 1984; for strictly isometric contractions); and shown that with increasing strength of such synchrony, the tremor becomes progressively larger, and more regular, compared with the minimal tremor in the practical absence of synchrony (also see Logigian et al. 1988; Young and Hagbarth 1980).

These observations combined with theoretical considerations have indicated that at least two parallel neuronal mechanisms participate in the generation of physiological force tremor: the rhythmical discharges of the relatively large active MUs near their recruitment rate, as an inevitable cause of small (minimal) tremor within the respective frequency band, and a second mechanism, causing additional, synchronized (in-phase) MU firing rhythms, as a tremor source of variable involvement and weight.

Furthermore, the second tremor mechanism is probably spinal stretch reflex oscillations that are expected to occur in this closed-loop system because of both muscle and conduction delays and therefore have frequencies in the typical tremor range. Thus the small oscillations of internal muscle length caused by tremor are reflected through Ia afferent activity (Hagbarth and Young 1979; Kakuda 2000; Koehler et al. 1984) in synchronized oscillations in the membrane potentials of the MNs. This leads to synchronized rhythmic discharges of the cells, which cause a tremor component that is continuously reinforced. Importantly, MNs with firing rates higher than the tremor frequency, exhibit additional, interspersed spikes. An analogous behavior has been described in an intracellular study of respiratory activities (Huang et al. 1996).

In any given contraction, the strength of the MU synchrony determines the relative weights of the two parallel tremor mechanisms and thus influences the properties of tremor. As a result, tremor tends to be larger, and more regular, in the presence of a strong synchrony, i.e., when the synchronized tremor component dominates over the components of the large MUs.

At the same time, the central frequency of tremor is slightly, but consistently, higher when the effects of the large MUs dominate (e.g., during ischemia; Table 2). A simple explanation for this frequency similarity, and the associated small differences, is provided by the following preliminary observation in experiments where the voluntary muscle force was varied slightly and slowly around the recruitment threshold of MUs. Each MU, after a pause, resumed firing with spikes near the local minima of tremor in a one-to-one relation. Therefore MUs seem to have recruitment rates close to the loop frequency, reflecting the loop oscillations in the membrane potentials of MNs. Consequently, the central frequency of the tremor of the large MUs is expected to be close to, but higher than, the frequency of the loop tremor.

Similar recruitment rates of MUs, in the range of tremor frequencies, have been reported for various muscles (Henne-
Neuronal mechanisms of physiological force tremor: unification of two seemingly conflicting hypotheses

The above model of two parallel tremor mechanisms, namely large MUs and loop action causing MU synchrony, essentially unifies the two major hypotheses on tremor generation. These are widely considered mutually exclusive, because they are associated with seemingly conflicting observations and suggestions.

The original hypothesis that considered the intrinsic rhythmicity of MU firing as tremor cause (Marshall and Walsh 1956) was subsequently modified by Freund and colleagues (Allum et al. 1978; Dietz et al. 1976; Freund 1983) to include only the last-recruited, large MUs, which could be dominant and actually fire in the band of tremor frequencies. Short-term correlations of MUs were also implicated, in accord with the prevailing view that the tremor regularity implies MU synchrony. However, the issue of the synchrony remained open, given the limited evidence from MU/MU correlation measurements (Christakos 1982c). Moreover, Taylor (1962), using an electronic model of a few independent MUs, observed an apparent rhythmical grouping of MU spikes and proposed that tremor could be a chance phenomenon.

In support of this hypothesis, mathematical and simulation studies using a population model of muscle activity (Christakos 1982a,b,c; Christakos and Lal 1980) predicted the occurrence of tremor caused by the large MUs in the absence of MU synchrony (also see Clark et al. 1981). These studies also mathematically explained the rhythmical grouping of spikes of uncorrelated MUs, i.e., the electrical analog of tremor.

The other original hypothesis (Halliday and Redfearn 1956; Lippold et al. 1957), which attributed tremor to spinal stretch reflex oscillations causing a strong MU firing synchronization, was also objected to for such reasons as the absence of tremor when the reflex feedback to MNs is interrupted (e.g., Cussons et al. 1979; Marsden et al. 1967) and the usual lack of strong synchronization of MU discharges (see Christakos 1982c; Windhorst 1988). On the assumption that only conduction delays around the loop are involved, another important objection had to do with the similarity of the tremor frequencies in children and adults or in muscles at different distances from the spinal cord (Elble and Koller 1990; Marshall 1959). It should be noted that this assumption is still widely used, but it is invalidated by our results regarding the existence and prominence of the muscle delay.

This hypothesis received strong support from various experimental studies, notably those of Lippold (1970) and Hagbarth and Young (1979), as well as modeling ones using single- or multiple-feedback loop representations of the stretch reflex (Koehler and Windhorst 1981; Mori and Ishida 1976; Stein and Oguztoreli 1976).

It should be noted that in another original hypothesis, Elble and Randall (1976) attributed their observation of coherent tremor components of MU activities, under conditions of large and regular tremor, to action of the Renshaw cell population. This hypothesis has also been associated with contradictory evidence. Indeed, certain studies have indicated desynchronizing effects of Renshaw cells on alpha-MNs (Adam et al. 1978; Mallenfort et al. 1998), whereas a recent one (Mattei et al. 2003) has revealed a synchronizing such influence of Renshaw activity in the case of a forearm muscle. In this context, it is important to note the more encompassing view of Windhorst (1996) in his extensive report on the role of Renshaw cells in motor control (also see Windhorst 1984). In any case, it should be stressed that the hand muscle studied here (FDI) lacks recurrent inhibition (Katz and Pierrot-Deseilligny 1999; Mattei et al. 2003).

As a consequence of such seemingly conflicting evidence and suggestions, the tremor issue has not yet been settled, and either of the above two major hypotheses is usually adopted in tremor studies.

Thus the large MU hypothesis was used in a variety of more recent studies, including studies of sustained contractions, effects of aging or handedness, and attention demanding tasks, (Galganski et al. 1993; Loscher and Gallasch 1993; Schmied et al. 2000; Semmler and Nordstrom 1995, 1998; Semmler et al. 2000a,b). In some of these studies, the short-term MU synchronization was found to be weak. In view of the present results, it seems likely that the large MUs indeed were the main contributors to the tremor in those cases of limited MU synchrony.

It should be noted, however, that the short-term synchronization (measure of approximate spike coincidences) is not an appropriate index of rhythmical synchrony (Christakos et al. 2003). A related study by Semmler et al. (2003) using MU/MU coherence analysis indicated the superiority of such analysis in detecting and quantifying the tremor synchrony. In fact, the observed coherences between MUs in that study revealed the presence of some MU synchrony in the tremor band and hence a corresponding contribution to tremor.

In other recent studies, the monosynaptic stretch reflex loop was implicated in tremor generation. Thus Timmer et al. (1998), in a modeling study, found a significant role of reflexes in enhanced tremor, and Cresswell and Loscher (2000) showed an important involvement of large fiber (probably Ia) afferent feedback in tremor enhancement under conditions of muscle fatigue. More generally, Matthews (1997) proposed that a mismatch within the loop, between MU firing rate and speed of contraction of its fibers, may be a cause of tremor, whereas Windhorst et al. (1994) concluded that the action in the MN/muscle spindle loop and that in the MN/Renshaw cell loop may combine to decrease the likelihood of tremor.

Our model, by combining these two tremor mechanisms, 1) suggests direct answers for the aforesaid criticisms regarding the two major tremor hypotheses and provides explanations for observed tremor features, and 2) enables the specification of the conditions under which one or the other mechanism dominates, but also covers a wide range of intermediate situations where both mechanisms have significant contributions to tremor.

With respect to 1), this model explains the occurrence of tremor, caused by large MUs, when the loop is interrupted and there is no MU synchrony; the similarity of the tremor frequencies in muscles for which the conduction delays around the reflex loop are grossly different, because the total delay of the loop is mainly caused by muscle delay; the 6- to 12-Hz range of tremor frequencies, for the same reason; and the
lengthening of the tremor period in cooling experiments (Lippold 1970), because of the associated increase in the muscle delay. Finally, through the hypothesized link between MU recruitment rate and loop frequency, this model could explain the common observation of a relatively fixed tremor frequency for each muscle.

Regarding 2), this model indicates that a contribution to tremor from the large MUs is always present. This contribution dominates when the action of the loop is limited, giving rise to small tremors within the band of firing rates of the particular MUs. According to the relationship shown in Fig. 6, this was the case in our study for a small fraction of contractions exhibiting MU/force coherences <0.10, or, equivalently, MU/MU coherences <0.01. On the other hand, for a strong action of the loop, the loop’s contribution becomes dominant, and the tremor is large and regular. Such force tremors can be as large as 15% of the mean force and could be classified as “enhanced.” According to Fig. 6, this occurred in a small fraction of the studied contractions, for which the MU/MU coherence was above −0.35 and was apparently associated with a very large Ia input to the MN pool.

However, for the majority of contractions, where the MU/force coherences were within 1 SD from the average coherence in our sample, and the respective MU/MU coherences were between 0.03 and 0.25, both mechanisms had significant contributions to tremor.

The existence of contractions with different degrees of MU synchrony and different tremor properties for each individual emphasizes the role of such factors as spindle sensitivity and efficacy of spindle action on alpha-MNs. Different settings of such parameters could underlie the different tremor and MU activity states. For example, stress is thought to increase the MU synchrony and the tremor amplitude through enhanced spindle feedback, and, similarly, enhanced tremor under conditions of hyperthyroidism, aging, and fatigue is assumed to be a consequence of increased MU synchrony (McAuley and Marsden 2000; also see Cresswell and Loscher 2000; Semmler et al. 2003).

It should be noted that Lakie et al. (2004) reported a reduction of the tremor amplitude after 2 min of ischemia, accompanied by an elevation of interstitial potassium concentration, and proposed that the reduction mechanism is muscular rather than neural. However, such effects at the muscle level could not account in any simple way for the suppression of the MU synchrony that we observed in our experiments, and seem to act as an additional mechanism influencing the tremor amplitude. Furthermore, a partial block of Ia afferents during the first few minutes of ischemia could underlie the small tremor reduction observed by Lakie et al. (2004) compared with the drastic reduction we observed when the Ia block was nearly complete after 10 min of ischemia (Schnitzler et al. 1997).

The above two parallel mechanisms of force tremor in steady contractions are probably responsible for the neuronal component of the postural tremor of extremities, i.e., the tremor component that does not depend on limb mechanics (Stiles 1980).

Finally, we recently showed the presence of an involuntary, fast force oscillation during slow sinusoidal voluntary muscle contractions (Erimaki and Christakos 1999; Papadimitriou et al. 2003). For each subject, this oscillation had the same frequency as the subject’s tremor in constant strength contractions, and its properties had a similar dependency on MU synchrony as those of the latter tremor. Moreover, ischemia had the same effects on the oscillation and the synchrony as in the case of steady contractions. It therefore seems probable that the same two parallel mechanisms underlie force tremor in varying strength muscle contractions. These mechanisms are also expected to cause tremor during movement, i.e., an imposed oscillation analogous to action tremor.

Possible supraspinal tremor sources

Supraspinal tremor sources causing MU synchrony have also been hypothesized, including the inferior olive (Llinas and Yarom 1986) and, recently, the motor cortex or other subcortical structures (see arguments presented by McAuley et al. 1997; Raethjen et al. 2000; Vaillancourt and Newell 2000).

In general, the direct supporting evidence has been the observation of weak corticomuscular (ATA) tremor (6–12 Hz) coherences in certain studies (Marsden et al. 2001; Mima et al. 2000; Salenius et al. 1997) and substantial such coherences in one study with epileptic subjects (Raethjen et al. 2002). It should be noted that other studies found no corticomuscular coherences in the 6- to 12-Hz range (Conway et al. 1995; Farmer et al. 2004; Halliday et al. 1998; Hansen et al. 2002; Kilner et al. 1999; Mima and Hallet 1999). This, however, could not be used as an argument against a cortical influence on tremor.

As described in METHODS, estimates of coherence between population aggregate activities are not related in any simple way to the true coherences between units of the two populations (Christakos 1997). In particular, such estimates are expected to give an overrated picture of tremor synchrony within the muscle but may also do the same for the synchrony between muscle and cortex. Therefore even high corticomuscular tremor coherences could not be used as conclusive evidence for a substantial synchrony between MU populations and cortical cell populations.

The observations of Baker et al. (2003) regarding the very limited coherence of individual pyramidal tract neuron (PTN) activities to rhythmical local field potentials in the cortex, and to one another, are in accord with this view. As concluded by these authors on the basis of simulation results, the cortical rhythms can still be faithfully transmitted to alpha-MNs by the population of practically uncorrelated PTNs (also see Christakos 1986). Clearly, such rhythms at the level of MNs will also be practically uncorrelated, unless an additional, possibly interacting, mechanism, like the loop action, causes MN synchrony or amplifies the limited input synchrony.

There exists, however, one condition under which ATA coherence computations can lead to an underestimation of the strength of the tremor synchrony between an MU population and a cortical population. As explained in METHODS, this occurs
if in the cortical population there exist uncorrelated rhythms around the tremor frequency that dominate the recorded activity and thus suppress the ATA coherence. This is a worthwhile examining possibility.

In conclusion, our results, and particularly our observations during ischemia, strongly suggest that Ia afferent feedback is an essential element of the generator of tremor or at least a necessary trigger input to it. Given this, the participation of the associated muscle element in the generator seems inevitable, because each grouped spindle discharge during force tremor occurs around a specific time in the phase of muscle lengthening. Thus the monosynaptic stretch reflex loop seems to be a main source, or at least a significant part of the generator, of the force tremor and the accompanying rhythmical synchrony of the MUs.

At the same time, the existence of supraspinal generators of synchronous rhythms that are manifested as tremors at the periphery cannot be ruled out as a result of our observations. In fact, the remaining weak synchrony in some of our ischemia tests may well be caused by an incomplete Ia afferent block, but it could also reflect some contribution from other sources of synchrony, such as supraspinal ones. Depending on how strong the impact of such generators is, monosynaptic stretch reflex loops would play, through interactions, an important role in determining the tremor frequency and other properties, by “filtering” such correlated inputs to the alpha-MNs and amplifying the input synchrony. Furthermore, Ia afferent activity could then act as a trigger to such generators.

It is important to note that in slowly varying, voluntary muscle contractions, the modulation of MU firing and the associated synchrony still exist under conditions of ischemia, where the tremor synchrony is practically absent (Erimaki and Christakos 1999; Papadimitriou et al. 2003). Because such modulations and synchrony are likely of cortical origin, these differential effects of ischemia provide additional support for the view that the main generator of tremor and its synchrony is not at the cortical level.

It seems therefore plausible that cortical rhythmicities showing some coherence to muscle tremors simply reflect tremor-related spindle rhythmicities projected to higher brain areas. Such cortical rhythms could be projected back to the alpha-MNs, in accordance with the reported signal transmission from the cortex to the muscle by Raethjen et al. (2002). They might even play a role in motor coordination and sensorimotor integration (Bernstein 1967; McAuley and Marsden 2000).

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