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The timing of primary orthostatic tremor bursts has a task-specific plasticity

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Summary

Primary orthostatic tremor is characterized by unsteadiness and shakiness of the legs while standing. It is due to a remarkably strong and regular EMG modulation at ~16 Hz that is thought to be of CNS origin. Previous studies have shown that the tremor frequency is the same in all involved muscles and that the time relation between bursts of activity in different muscles may be fixed (e.g. always co-contracting or always contracting in an alternating pattern). Here we have used frequency domain analysis of postural muscle EMG signals in five primary orthostatic tremor patients and in two normal controls to explore the nature of such fixed timing patterns. The timing is found not to relate simply to the relative conduction times for passage of rhythmic bursts from a central oscillation to different muscles. Indeed, although the timing pattern (expressed as phase) of the 16-Hz EMG bursts in different postural muscles remains constant while the subject adopts a certain steady posture, it is different for different subjects and also changes when the same subject adopts a different posture. It seems unlikely that such complex task-dependent timing relations of rhythmic postural muscle activity are due to the primary pathology of primary orthostatic tremor. Instead, we suggest that the abnormally strong peripheral manifestation of a 16-Hz CNS oscillation merely unmasks normal central processes so that the timing patterns may provide a clue to the nature of postural motor control.

Keywords: primary orthostatic tremor; coherence; phase

Abbreviation: FFT = fast Fourier transformation

Introduction

Primary orthostatic tremor is a rare neurological condition that results in unsteadiness and shaking of the legs while standing. The symptoms rapidly disappear on walking or on sitting down and no other neurological abnormalities are present. The tremor is associated with a uniquely strong and regular 16-Hz EMG modulation in leg muscles during postural muscle activity (Heilman, 1984; Thompson *et al.*, 1986). Such oscillations are considered to arise centrally (Britton *et al.*, 1992; McManis and Sharbrough, 1993; Wills *et al.*, 1994), although the nature of this central oscillation has not been explored in detail. Electrophysiological investigations of primary orthostatic tremor have indicated a linking of the timing of the 16-Hz EMG bursts between muscles (Thompson *et al.*, 1986; Britton *et al.*, 1992; McManis and Sharbrough, 1993), suggesting that they may derive from a single shared central rhythmicity, but there is confusion as to whether the oscillations are in phase (resulting in co-contracting muscles), out of phase (resulting in alternating contractions) or of variable phase. This study resolves these issues by performing a quantitative analysis in the frequency domain of the oscillations occurring in many simultaneously active muscles.

Previous studies have indicated that many other physiological and pathological tremors may be a manifestation of oscillations in the CNS and it has been suggested that such oscillations may have a role in motor control (McAuley *et al.*, 1997; Welsh and Llinás, 1997; Farmer, 1998). Direct recordings of central oscillations in the animal (Murthy and Fetz, 1992; Welsh *et al.*, 1995; Baker *et al.*, 1997) and in the human (Ribary *et al.*, 1991; Salmelin and Hari, 1994; Farmer, 1998) have shown that the presence and degree of synchronization of CNS oscillations depends upon the motor task being performed at the time, suggesting that linking of oscillations may play a part in the processing of motor commands. On the basis of multi-electrode Purkinje cell recordings in the rat, Welsh and Llinás have postulated that phase-locking of 6–10-Hz oscillations arising from the inferior olive may enable dynamic linking of certain groups of olivary outputs to the cerebellum (Welsh and Llinás, 1997). Such linking appears to be task-specific and may

Table 1 *Patients used in the study*

Case	Age (years)	Sex	Duration (years)	Main complaint	Beneficial medication	Frequency (Hz)* (mean ± SD)
1	58	F	2+	Unsteadiness and tremor on standing	Clonazepam	15.8 ± 0.35
2	65	M	4	Unsteadiness on standing still	Primidone	14.9 ± 0.59
3	64	F	5	Unsteadiness on standing	–	16.6 ± 0.47
4	53	F	6	Difficulty with balance on standing	Clonazepam	17.8 ± 0.27
5	46	F	5	Unsteady on standing and shaky legs	–	17.7 ± 0.31
						16.6 ± 1.16†

F = female; M = male. *Frequency refers to the mean value of the median frequency (determined to the nearest 0.25 Hz) of the EMG spectral peak averaged over all the muscles tested and over all trials performed by that subject; †overall mean.

therefore help the cerebellum to co-ordinate the activity of different muscle groups involved in a certain task. Since primary orthostatic tremor results in a uniquely strong and regular peripheral manifestation of a central oscillation, this condition may provide a relatively easy way in the human of exploring the nature of linking of a central oscillation that simultaneously modulates the activity of different muscles. Therefore, to address the broader issue of the role of central oscillations in motor control, the present study explores the task-specific nature of the linking of primary orthostatic tremor oscillations by making detailed measurements of any changes in the patterns of oscillation in different muscles during different postural activities.

It is found that, in primary orthostatic tremor, a linking does indeed exist between the 16-Hz range EMG oscillations of different muscles. The linked oscillations have a complex pattern of phase lags between these muscles that does not simply reflect the different motor conduction times from a single central oscillator down the descending pathways to different muscles. The pattern varies between subjects and on performing different postural tasks but is constant if a subject repeatedly performs the same task. The complex pattern of timing could represent the unmasking of normal processes that become peripherally manifest as a result of the abnormally strong 16-Hz central oscillation. Such timing relations could reflect the passage of motor commands through complex CNS neural networks that are relatively fixed while performing a certain task but vary for different tasks. Alternatively, as will be discussed, they may represent a more active process where the postural motor system controls linkages between muscles through a phase-dependent code.

Methods

Experiments were performed on five patients with primary orthostatic tremor (Table 1) and on two normal subjects. Informed consent was obtained from each subject and the study was performed with local ethical committee approval (Institute of Neurology, Queen Square). All patients were studied while off any anti-tremor medication.

Set-up and recordings

Polymyographic recordings were made on each subject while engaged in different postural activities. Silver/silver chloride 9-mm surface electrodes were applied over the motor point of a variety of different muscles. Those muscles simultaneously recorded included the cervical paraspinals, anterior deltoids, triceps, forearm flexors, quadriceps femoris, tibialis anterior and medial gastrocnemius, all on the right and left sides. The EMG signals were amplified by a Digitimer D (Welwyn, UK) amplifier and filtered with a low-pass first order Digitimer (–3 dB/octave) filter set at 100 Hz to minimize power at frequencies above the Nyquist frequency for Fourier analysis. A high-pass first order filter was set with a 3-ms time constant to prevent artefactual frequencies due to electrode movement from appearing in the EMG records. The signals were initially stored in analogue form on magnetic tape (Racal V-Store, Southampton, UK).

For analysis, the data were then digitized with 12-bit resolution by a 1401-plus (CED, Cambridge, UK) analogue-to-digital converter and digitally full-wave rectified. Sampling was performed at 512 Hz. Such a filtering and sampling procedure removes the higher frequency components from the EMG signals resulting from the spikes within each polyphasic burst. However, since each burst occurred at only 16 Hz or slower, the envelope of each burst would be well preserved and this envelope was the feature of interest in this study. To confirm the validity of this argument, some trials were performed on a pair of EMG signals applying a sixth order low-pass filter at 1 kHz and sampling at 2 kHz. The resultant power spectra were no different in the 0- to 100-Hz range from spectra derived after filtering and sampling the same stored data in the standard manner. The signals were displayed and stored on computer disc by a software package (CED Spike 2) running on an IBM PC microcomputer.

To record the tremor frequency of a limb, a small piezo-resistive accelerometer (Vibro-Meter SA105) was sometimes attached over the patella so that its direction of detection corresponded to an anteroposterior movement. The accelerometer weighed 6 g and had a linear range of acceleration response up to 200 ms^{-2} and a linear frequency response

range of 0–200 Hz. The accelerometer signal was high-pass filtered with a 300-ms time constant and digitally sampled at 512 Hz.

Protocol

Trials were conducted over periods of 2–2.5 min or for as long as the subject could maintain the posture before fatiguing or losing balance. In all, 56 trials were analysed. During a trial, subjects attempted to maintain a posture as steadily as possible. Postures included (i) standing still with feet apart; (ii) when possible, standing with feet together; (iii) walking on the spot; (iv) standing with both arms outstretched horizontally in front of the body; (v) leaning at ~60° to horizontal with the heels on the floor and supported by the outstretched arms holding a rigid vertical bar at chest height; (vi) on all-fours with weight evenly distributed between the palms of the hands and the balls of the feet; and (vii) crawling on the spot in the previous position. For formal determination of effects of posture, each patient performed at least three trials standing still and three on all-fours while recording right and left quadriceps and tibialis anterior. Trials were conducted in a random order, sometimes repeating the same trial, and between each trial was a rest period where the subject sat down on a chair for ~2 min. Unsteadiness or increasing discomfort prevented complete recordings of each trial in each patient; however, a good range of the above postures was recorded in all the patients.

Analysis

After initial inspection of the EMG signals for level of activity and for the presence of 16-Hz range bursts (Fig. 1), the data were analysed in the frequency domain by spectral analysis. The techniques used were similar to those employed previously (McCauley *et al*., 1997). Finite fast Fourier transformation (FFT) was performed on each EMG trace using a commercial software package (CED Spike 2). The block size for each FFT was set at 1024 points (2 s) which gave a bin width of 0.5 Hz. The power spectrum was then obtained by summing the squared real and imaginary components of the FFT. Each spectrum was averaged over ~60 contiguous FFT blocks to give the final overall power spectrum for that EMG trace and that trial. Artefacts in analysis resulting from the non-cycling nature of the data blocks were dealt with by the standard technique of applying a raised cosine window to each FFT block (Hanning) and compensating for the resultant loss of power. This procedure results in a high level of power in the first two frequency bins but the frequencies of interest were well outside this range. The *y*-axis of the spectral plots was root-mean-square power, equivalent to the variance of signal amplitude (i.e. a 'square of signal amplitude' parameter).

Coherence analysis (Jenkins and Watts, 1968) was performed between the EMG traces of every combination of muscle pairs in each trial to check for a match between the frequency peaks in their respective power spectra. An upper 95% confidence threshold line was calculated for non-zero coherence by the standard statistical method (Farmer *et al*., 1993). The phase differences between the coherent frequencies were determined by a separate program running in the Spike 2 environment which calculated the difference between the arctangents of the ratios of the imaginary and real components of the FFT at each frequency.

For each trial, a cycle diagram was constructed to illustrate the relative timings of the EMG bursts in the different muscles during the 16-Hz cycle of primary orthostatic tremor. This was done by measuring the phase lag between the coherent oscillations of each combination of two muscles and calculating the corresponding time difference. If eight different muscles were simultaneously recorded, this would give a total of 28 independently analysed and measured coherence and phase plots. These values were then used to determine the order of occurrence of bursts in each muscle within a cycle (Table 2). By relating all the different combinations of muscles together, seven different values were calculated for the time lag between two muscles whose EMG burst timings lay next to each other in the order of occurrence. The cycle diagram was finally constructed using the mean of these seven time lag values for each of the eight muscles. Right quadriceps femoris was arbitrarily placed in the 12 o'clock position.

Results

Subjects

All the patients studied (Table 1) had the characteristic clinical and electrophysiological features of primary orthostatic tremor (Britton *et al*., 1992). Their symptoms were of unsteadiness or muscular discomfort when standing, rather than merely of tremor or shaking. Neurological examination was normal apart from the presence of an unsteady and broad-based stance. The raw EMG records revealed rhythmical polyphasic bursts of ~60 ms period, corresponding to the typical 16-Hz rhythm. This rhythm was present in a variety of different muscles and more pronounced in the legs than in the arms. When standing, the strength of the modulation in some leg muscles was so great that very little EMG activity occurred between the bursts. The modulation strength became reduced when walking, especially during the swing phase (Britton *et al*., 1992; McManis and Sharbrough, 1993) and was absent when sitting down. The EMG bursts appeared almost immediately on rising to a standing position but it took a few seconds before the patient began to experience unsteadiness or tremulousness. In contrast, both the EMG bursts and symptoms disappeared rapidly as soon as the patient sat down.

Power spectra

Frequency analysis of EMG records revealed very sharp peaks at around 16 Hz in the power spectra, sometimes with

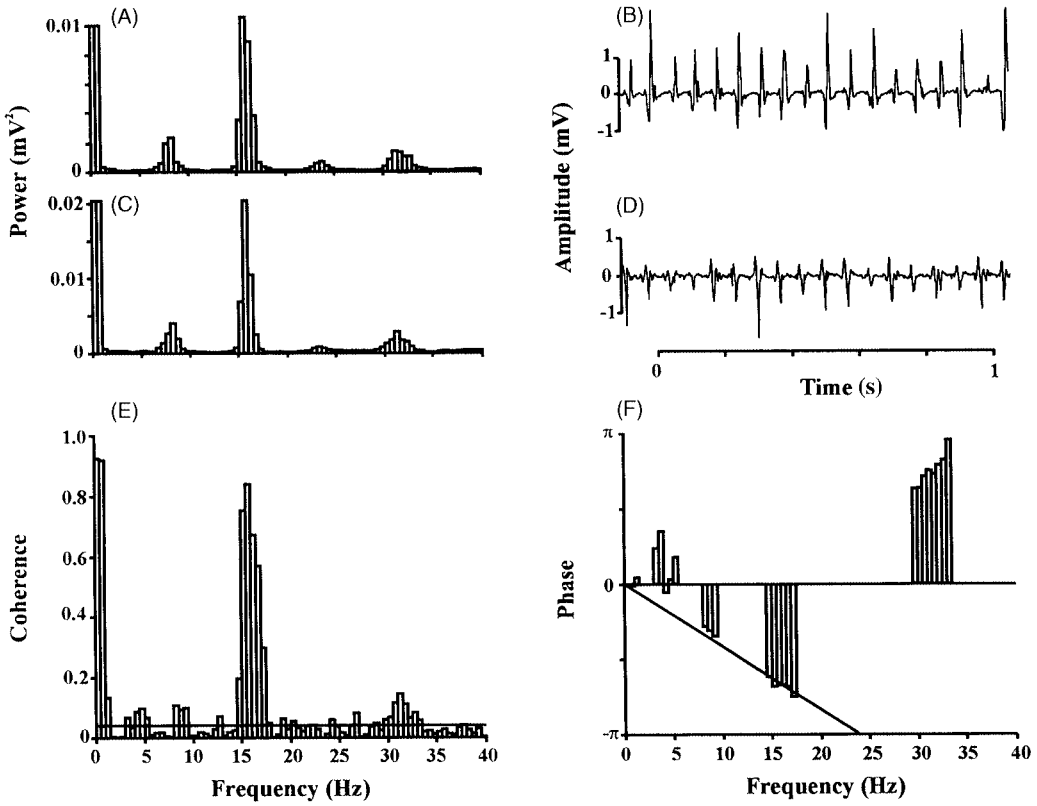

Fig. 1 Spectral analysis of 150 s of EMG from case 1 during stance. The power spectra (**A**) and unrectified filtered EMG (**B**) of right quadriceps and of left quadriceps (**C** and **D**) show a powerful modulation of ~16 Hz. The coherence plot (**E**) has a horizontal line indicating the 95% confidence level for significant non-zero coherence. There is extremely strong coherence between the modulations; the 16-Hz peak coherence has a *P*-value of 1.07×10^{-61}. From the slope on the phase plot (**F**) from the origin to the phase lag at the coherent frequency of ~16 Hz, the time lag of right behind left quadriceps is 20 ms. Only phase bins where there is significant coherence are shown.

smaller additional peaks at 8 Hz and at multiples of 16 Hz. Peaks at harmonic frequencies did not correspond to bursting in raw records at those frequencies; they were instead likely to be harmonics occurring because the envelope of EMG modulation was not exactly sinusoidal in form. On the other hand, the 8-Hz subharmonic peak did correspond to alternating large and small 16-Hz bursts in the raw records. In some records of arm muscles, 8 Hz was the dominant frequency of oscillation.

The mean (± standard deviation) frequency of the 16-Hz range EMG spectral peak averaged over all muscles and over all trials is shown in Table 1 for each subject. The values were estimated from the power spectra to the nearest 0.25 Hz. The variation was clearly greater between subjects than within a subject.

Coherence analysis

The 16-Hz range oscillations were generally very strongly coherent between all combinations of pairs of muscles (Fig. 1). This indicated that, over the whole 2-min period of a recording trial corresponding to nearly 2000 16-Hz cycles, EMG bursts in the two muscles were of the same frequency, had a constant phase relationship (i.e. constant relative timing) and had an unchanging relative strength of 16-Hz modulation in the two signals. The strong coherence implied that the same oscillator was driving the EMG bursts in different muscles.

The strength of coherence was greatest between those muscles that were most important in maintenance of the posture. When standing, coherence was strongest among the quadriceps and tibialis anterior muscles on either side of the body, but when crouching on all fours, muscle pairings giving strong coherence also included the triceps. The strength of coherence did not solely relate to the strength of activation of the muscles; this activation had to be in the context of the postural task. For example, the strength of coherence between arm muscles was only modest (but still often significant) during a standing trial, whether or not the arm muscle was additionally activated by lifting an object or by clenching the fist. On the other hand, when the arms supported the weight during a leaning or a crouching on all fours trial, coherence involving the arm became very strong. These results demonstrated that the 16-Hz oscillation was preferentially manifest during posture-related activity. Non-postural voluntary activity generated the typical EMG interference pattern which became manifest in addition to the ongoing

Table 2 *Relative time delay values (in milliseconds) determined from phase spectra of 16 Hz-EMG oscillations in all combinations of muscle pairs during a single trial performed by one subject (case 2)*

Muscle*	Rq	Rg	Lta	Ld	Lq	Rta	Lg	Rd
Rq	–	23.3	26.3	27.5	35	55.9	64.2	65.9
Rg	43.4	–	1.8	1.9	12.5	33.7	40	42.5
Lta	40.4	64.9	–	1.3	9.6	29.6	37.9	38.4
Ld	39.2	64.8	65.4	–	7.3	28.2	37.2	37.1
Lq	31.7	54.2	57.1	59.4	–	19.6	29.2	30.4
Rta	10.8	33	37.1	38.5	47.1	–	9.6	10.8
Lg	2.5	26.7	28.8	29.5	37.5	57.1	–	0.4
Rd	0.8	24.2	28.3	29.6	36.3	55.9	66.3	–
	Rq–Rg	Rg–Lta	Lta–Ld	Ld–Lq	Lq–Rta	Rta–Lg	Lg–Rd	Rd–Rq
	23.3	3	1.2	7.5	20.9	8.3	1.7	0.8
	24.5	1.8	0.1	10.6	21.2	6.3	2.5	0.9
	25.6	0.6	1.3	8.3	20	8.3	0.5	2
	22.5	2.9	2.3	7.3	20.9	9	−0.1	2.1
	22.2	4.1	1.4	8.6	19.6	9.6	1.2	1.3
	24.2	2.1	0.7	8	19.6	9.6	1.2	0
	23.4	4.1	1.3	6.7	19.6	10.4	0.4	2.1
Mean (± SD)	24 ± 1.19	3 ± 1.27	1 ± 0.67	8 ± 1.26	20 ± 0.72	9 ± 1.33	1 ± 0.88	1±0.80
	Rq	Rg	Lta	Ld	Lq	Rta	Lg	Rd
MCT	23.5	30.6	30.7	10.6	23.5	30.7	30.6	10.6
	Rq–Rd	Rd–Rg	Rg–Lta	Lta–Lq	Lq–Ld	Ld–Rta	Rta–Lg	Lg–Rq
Mean – MCT	12	4	4	17	5	8	8	11

The timings are listed in their order of occurrence, starting arbitrarily with right quadriceps. For example, the first row, labelled Rq, shows the measured delays from right quadriceps to the other seven muscles. In the lower half of the table, values are then calculated for the time difference of 16-Hz pulses between consecutive muscles in the order of occurrence. Thus, seven values are obtained for right quadriceps to right gastrocnemius by subtracting values in the Rg row from the Rq row. The means of these seven values and their standard deviations are shown, together with the different values and order of occurrence at the level of central output when the extra delays due to total motor conduction times (determined by transcranial magnetic stimulation) are subtracted from each muscle. The means are rounded to zero decimal places because the sampling frequency of 512 Hz means that accuracy cannot be achieved beyond the order of 1 ms. MCT = motor conduction time (milliseconds). *Rq = right quadriceps; Rg = right gastrocnemius; Lta = left tibialis anterior; Ld = left deltoid; Lq = left quadriceps; Rta = right tibialis anterior; Lg = left gastrocnemius; Rd = right deltoid.

primary orthostatic tremor pulses; however, the latter did tend to become reduced in amplitude during simultaneous voluntary activity.

8-Hz arm tremor: subharmonic oscillation or concurrent essential tremor

When the involvement of arm muscles in posture was relatively modest, e.g. when the arms were held outstretched for balance, the dominant modulation of the EMG was sometimes at 8 Hz (Fig. 2). However, despite this, the coherence between the two arm muscles was often stronger at 16 Hz than at 8 Hz and was primarily at 16 Hz between an arm and a leg muscle. There was a similar phase relationship of the coherence at the two frequencies (a single straight line from the origin cut through the phase values of both coherent frequencies). These findings suggested that the 16-Hz and 8-Hz oscillations were harmonically related rather than independent. Thus, the presence of an 8-Hz oscillation in the arm did not necessarily imply the presence of dual pathology, namely essential tremor occurring concurrently with primary orthostatic tremor; instead, the 8-Hz arm oscillation was easily explained as a subharmonic of the widespread 16-Hz oscillation.

Phase analysis

The phase plots, which show quantitatively the phase differences between coherent oscillations, usually revealed that the rhythmic EMG bursts of pairs of muscles were neither co-contracting (zero phase difference) nor contracting in alternating fashion (π radians phase difference). Instead, there was a range of phase values that varied between different muscle combinations and between the same muscle combinations in different subjects. In other words, although the relative timing of bursts between two muscles was constant within one trial to give strong coherence, this timing varied from one muscle pair to another and from subject to subject.

Table 2 shows the pattern of time lags for a single trial performed by one subject. Eight different muscles were simultaneously recorded so all combinations of muscle pairs resulted in a total of 28 coherence and phase plots. Each phase plot was an accurate measure of burst timing since the calculations were derived from the overall pattern of nearly

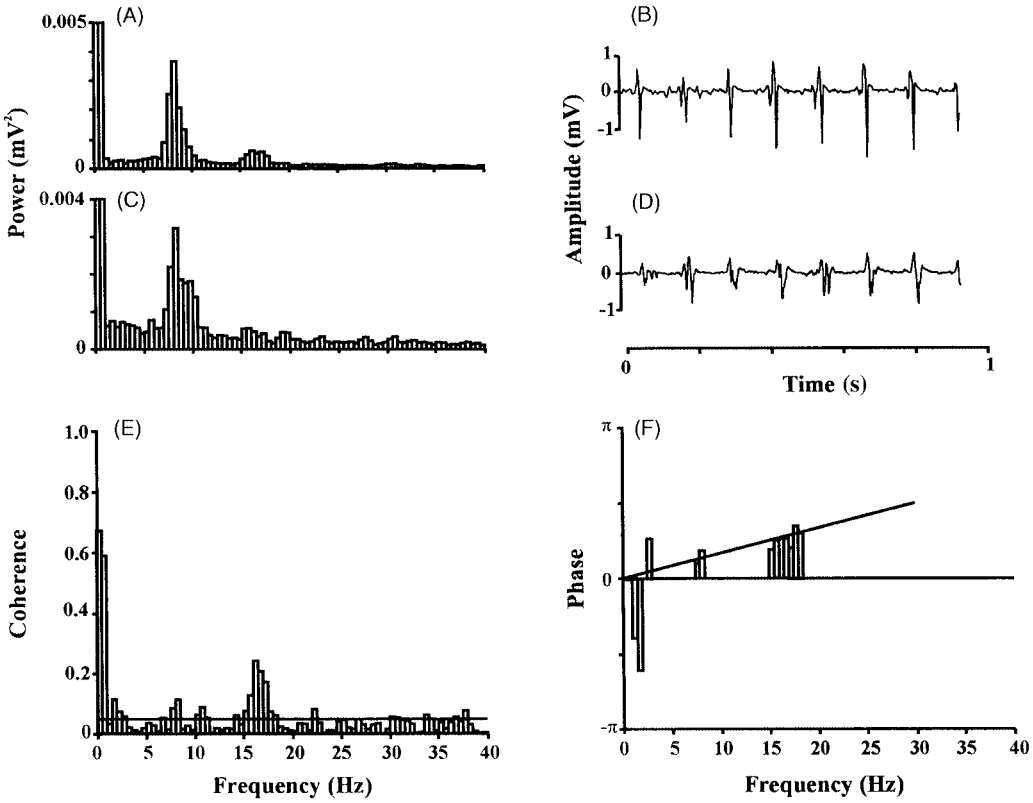

Fig. 2 Spectral analysis of 150 s of EMG from case 1 while standing with arms outstretched. The power spectra (**A**) and EMG (**B**) of right anterior deltoid and of left anterior deltoid (**C** and **D**) show a modulation mainly at ~8 Hz, but the greatest coherence is at ~16 Hz (*P*-value for the 16-Hz peak is 5.7×10^{-10}). From the phase plot (**F**), the right leads the left deltoid by 9 ms.

2000 EMG bursts during a 2-min trial. The 'average' time lag from an EMG burst in one muscle to that in the other was calculated from the phase plot by measuring the slope of a line from the origin to the bin values at the coherent frequency of ~16-Hz. The pattern of lags was consistent within a trial so that the EMG bursts in the different muscles occurred in a certain order; for example, in the trial shown in Table 2, the lag from right quadriceps to right gastrocnemius was around 23 ms whether determined by directly measuring the phase difference between these two muscles or by subtracting the right gastrocnemius to left tibialis anterior lag from the right quadriceps to left tibialis anterior lag. In this way the order of occurrence of all eight muscles could be determined and, by using the six indirect measures in addition to the direct one, seven different inter-dependent values could be obtained for the time lag between two muscles occurring next to each other in the sequence of bursts. Thus, when the values of time lags from right gastrocnemius to the other seven muscles (row 2 of Table 2) were subtracted from the corresponding values from right quadriceps to the other muscles (row 1 of Table 2), this gave seven values for the delay from right quadriceps to right gastrocnemius. The low standard deviation of these seven delay values illustrates the consistency of the pattern and the accuracy with which the time delays between EMG bursts could be determined.

Although the determination of time lags from phase plots assumes simple linear behaviour (e.g. a clear phase delay of $\frac{1}{2}\pi$ (90°) is equivalent to one-quarter of the total period), we feel this assumption is justified because of the high level of consistency when calculating the same time delays using several different phase plots. The extremely high levels of coherence (much higher than in most other neurophysiological systems) means that the phase plots (Figs 1 and 2) are likely to yield more reliable phase lag values.

Since coherence was present between all muscle pairs during a trial, the timing relationship between all the muscles had to be constant over this period. In order to examine this relationship more closely, cycle diagrams were calculated for each trial (see Methods). These diagrams gave the order and relative time of occurrence of EMG bursts of all the muscles during one 16-Hz cycle (Fig. 3A). There appeared to be no simple pattern governing the relationship.

An obvious explanation for non-simultaneous timing of the EMG bursts in different muscles would be the different lengths of time taken for impulses to pass from a central rhythm generator down the spinal cord to the different muscles. Therefore, the approximate figures (in milliseconds) for motor conduction times to the various muscles, as determined by transcranial magnetic stimulation (deltoid = 10.6, triceps = 13.2, forearm flexors = 15.2, quadriceps = 23.5, tibialis anterior = 30.7, medial

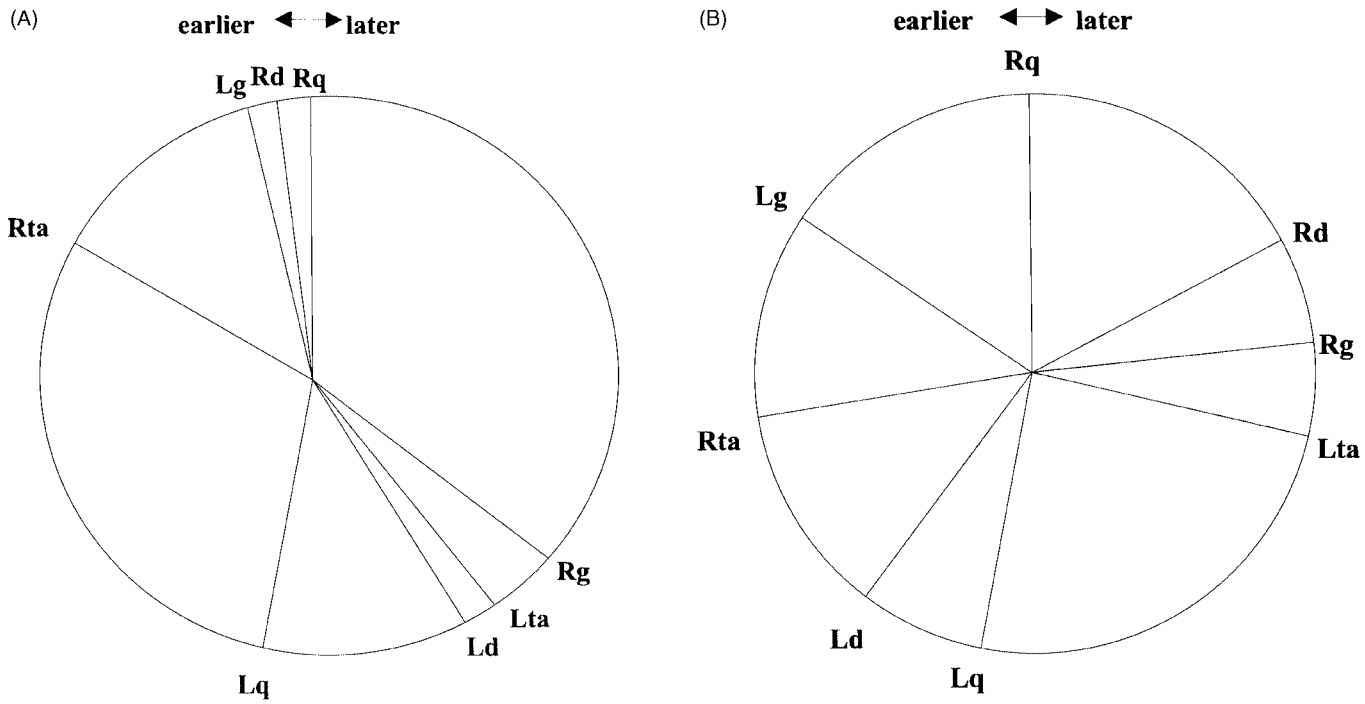

Fig. 3 Cycle diagram of timing relationships (**A**) of EMG modulation of right and left anterior deltoid (Rd, Ld), right and left quadriceps (Rq, Lq), right and left tibialis anterior (Rta, Lta) and right and left gastrocnemius (Rg, Lg) in case 2 while standing with arms outstretched. The same data are shown (**B**) where all the timings are shifted earlier by the motor conduction times of the different muscles, illustrating the central timing relationships of the modulation before it passes down the pyramidal tracts. If the timings of bursts in different muscles were simultaneous, the lines corresponding to the different muscles would all overlie right quadriceps (the arbitrary 12 o'clock position). The modulation is clearly not synchronous in different muscles either peripherally or when corrected for central conducting times. The data for this diagram are shown in Table 2.

gastrocnemius = 30.6; after Thompson, 1990), were subtracted from the values of the cycle diagrams (Table 2; Fig. 3B). However, there was still no clear concordance of EMG burst timings, showing that the timing relationship did not simply correspond to differences in conduction time from a single uniphasic oscillator in the brain to the different muscles via relatively direct spinal pathways. Examination of the cycle diagrams of all the subjects revealed that not only did the timings fail to match with those expected for such an oscillator but that the timings were completely different in different subjects (cf. Figs 3–5). This again argues against a simple fixed timing relationship of EMG bursts in different muscles.

Accelerometer recordings of leg tremor taken during periods of strong 16-Hz EMG rhythms revealed a surprisingly low power of tremor at 16 Hz. Such observations have been made previously (McManis and Sharbrough, 1993) and are corroborated by the fact that patients commonly report unsteadiness without tremor and by clinicians' lack of observation of tremulous leg movement. The tremor was stronger at subharmonic frequencies around 8 Hz. The low tremor amplitude, and especially its predominance at a different frequency, made it highly unlikely that the time lags between different muscle EMG bursts could be explained simply on the basis of spread of the 16-Hz EMG oscillation by reafference via peripheral feedback from afferent receptors that somehow respond selectively to 16 Hz tremor. Instead, the EMG modulations in all the muscles were likely to be directly driven by the CNS. The consistent and quite large change in phase relationship between the EMG bursts of different muscles for different subjects and on performing different tasks (described below) provides additional evidence for a central rather than reafferent origin.

Task-specificity

Further investigation of the timings between leg muscles in different trials performed by the same subject revealed that the timing pattern was task-specific. Those trials that involved similar leg postures, namely standing with feet together, standing with feet apart and standing with arms outstretched, all showed that the timing pattern, for the leg muscles only, was quite similar. On the other hand, when the subject was on all fours, the timing pattern was completely different. This occurred even when crouching on all fours trials were interspersed between standing trials (Fig. 4). So, when a subject stood, the timings of 16-Hz EMG bursts in different muscles consistently followed one pattern and when he crouched on all fours the timings consistently followed a different pattern. In all five patients, the above features of timing patterns were clearly evident when three standing trials were compared with three crouching trials (Fig. 5A

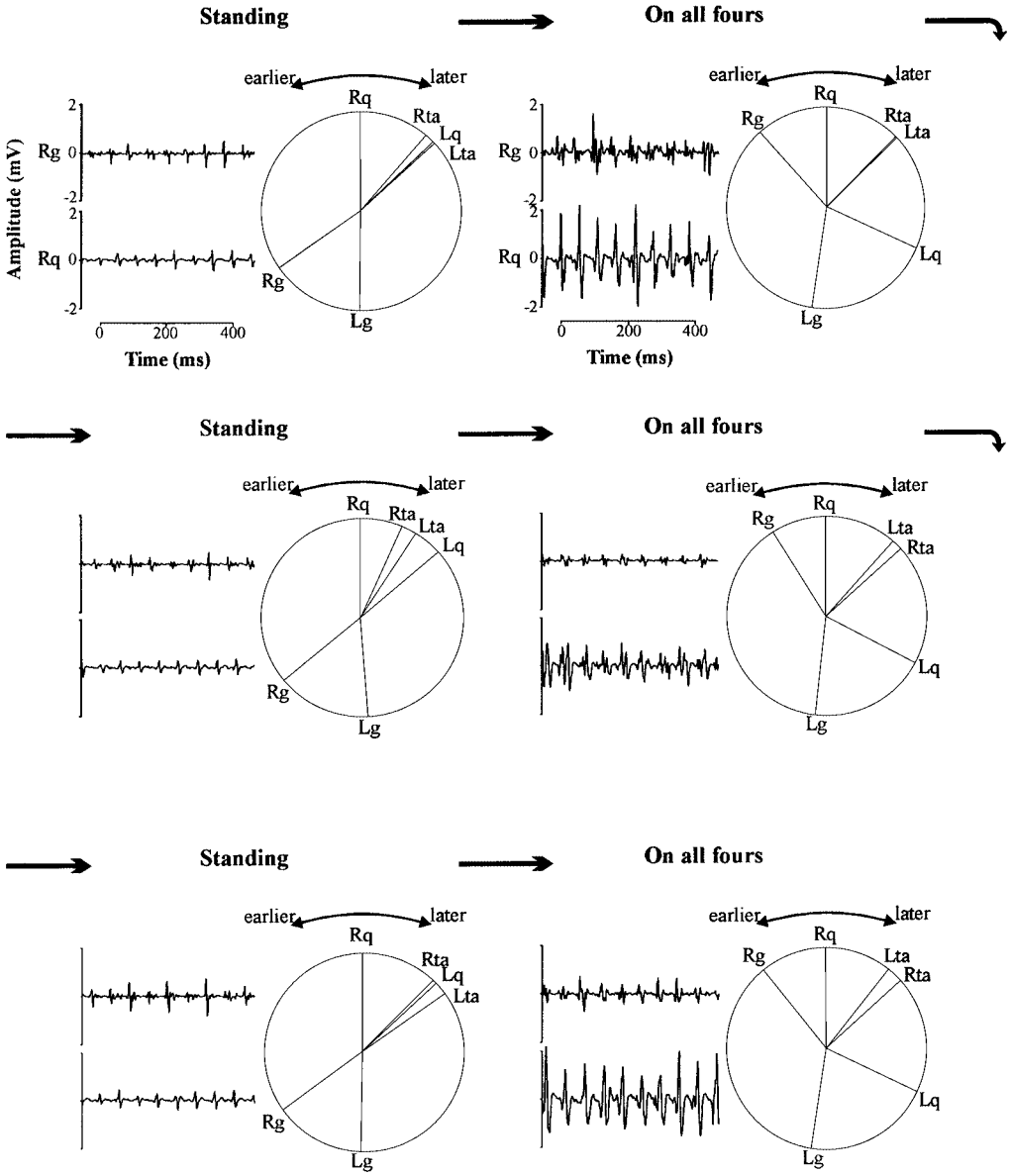

Fig. 4 Sections of EMG trace of right gastrocnemius and right quadriceps in case 4 while performing consecutive trials alternating between standing and on all fours trials. The bursts are more synchronous between these two muscles while adopting the on all fours posture. Cycle diagrams of timing relationships of EMG bursts of all the recorded muscles during these postures confirm the difference in patterns between the two postures, yet the relative consistency when returning to the same posture. The on all fours trials have a greater lag (relative to right quadriceps, Rq) for right tibialis anterior (Rta), left quadriceps (Lq), and left and right gastrocnemius (Lg, Rg), while there is overlap between the two postures for the lags to left tibialis anterior (Lta).

and B). The clear differences between patients as well as between different postures is also noted.

The mean (± standard deviation) separation between maximum and minimum values for the same posture over every muscle pair in every subject was only 2 ± 1.2 ms, while the mean separation between mean (not maximum and minimum) values for standing versus crouching postures was 13 ms. In fact, when comparing different postures, only in two out of 20 muscle pairings (five subjects, four muscles) was there any overlap between the three standing and three crouching values. For a 60-ms (16-Hz) cycle, two sets of values might be expected to overlap by random chance alone if the differences within the same posture are around 2 ms.

This constancy within postures and difference between postures was shown formally over the five subjects by a multivariate repeated measures analysis of variance of the main effects of trial and posture (using the Statistical Package for Social Sciences). The cycle diagrams allowed clear graphical comparisons to be made between trials, but data in this raw form were unsuitable for statistical verification. For

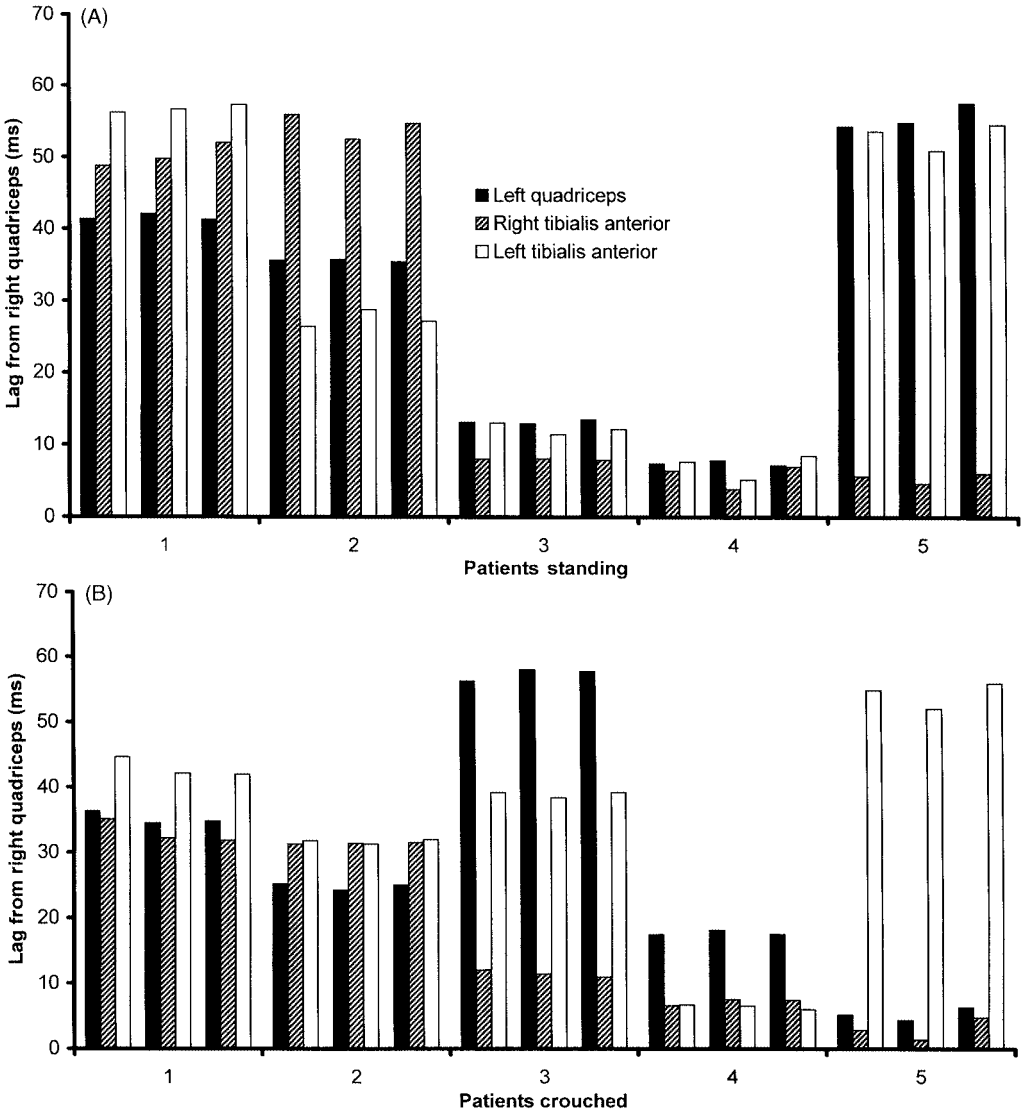

Fig. 5 Lags of timings of bursts in left quadriceps, and right and left tibialis anterior muscles behind right quadriceps in all five primary orthostatic tremor patients. In each patient three separate trials are displayed, showing how the pattern of burst timing is the same in the three repeated trials performed by the same patient but different in different patients. (**A**) shows the results for standing trials while (**B**) shows those for trials when crouched on all fours. It is clear that the pattern of lags is different for different postures.

example, in trying to determine if the timing between two muscles is different for two different postures, an artificially low mean difference would arise if half the subjects had a large increased lag when crouched compared with when standing and the other half had a large reduction in lag. A simple mean would erroneously indicate that there was little difference between postures. Therefore, the data were transformed to compare magnitudes of change in lag between the two postures; when a crouching trial had a smaller lag, the value was converted to be the same amount greater than the standing trial as it had been smaller. This was achieved by adding to the crouching trial twice the difference between the mean of the three crouching trials and the mean of the three standing trials. This resulted in an unchanged overall magnitude of difference and, most importantly, unchanged difference between the three individual trial values for the same posture. Negative (i.e. anticlockwise) separations between muscles were treated in the same way as positive values. These changes also had the effect of changing the essentially circular nature of the data to an approximately normal distribution. Some power in distinguishing standing from crouching trials is lost by removing the direction information, making statistical comparison more conservative. However, no power is lost in the detection of differences within the same trial.

There was indeed a significant difference in the four multiple measures of right quadriceps to left quadriceps, left quadriceps to right tibialis anterior, right tibialis anterior to

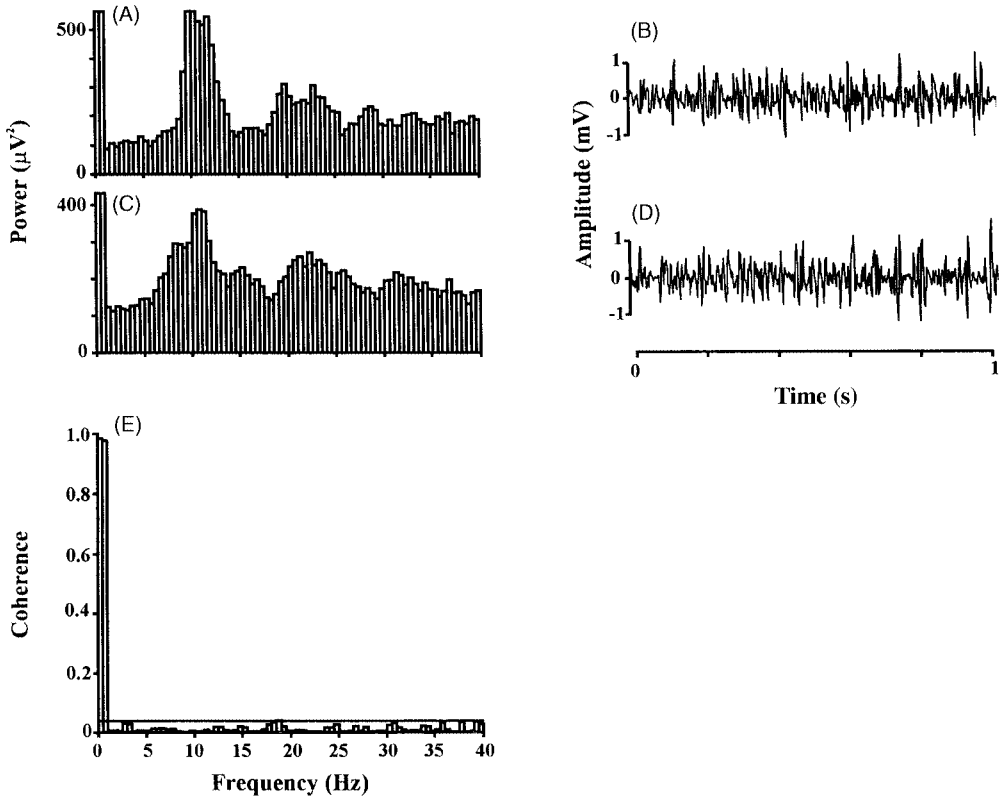

Fig. 6 Spectral analysis of 150 s of EMG from a normal subject while standing with knees a little bent. The power spectra of right quadriceps (**A**) and left quadriceps (**C**) show similar peaks of EMG power at around 10 Hz. The rhythmic modulation is much weaker than that of primary orthostatic tremor, as seen from the EMG traces of right quadriceps (**B**) and left (**D**) quadriceps. There is no coherence (**E**) between EMG signals.

left tibialis anterior and left tibialis anterior to right quadriceps between the two postures ($P = 0.024$) and no evidence for a significant difference between three trials of the same posture ($P = 0.991$, power = 0.07).

The consistency of timing relationship was maintained over a whole experimental session lasting up to 3 h. On re-testing one subject after 4 years, the pattern had changed somewhat to a different pattern but this new pattern was still consistent within an experimental session.

Normal subjects

Polymyography was similarly performed on two normal subjects. Frequency peaks were again present but they occurred from 10–15 Hz, a lower and more variable frequency range than that for primary orthostatic tremor. The peaks were also of lower power relative to the total spectral power. There was no significant coherence between any combination of muscle pairs in any trial, even though homologous muscles on either side of the body often had very similar power spectral peak frequencies (Fig. 6). This indicated that, even though the oscillations were of the same frequency, they existed independently and there was no phase linking.

Discussion

The nature and origin of primary orthostatic tremor

Earlier reports in the literature have sometimes confused primary orthostatic tremor with a variant of essential tremor that exhibits a 6–8-Hz leg tremor (Critchley, 1972). However, electrophysiology has shown that primary orthostatic tremor is a distinct entity, having a very strong posture-related 16-Hz tremor. On the basis of an increased incidence of essential tremor in first-degree relatives of patients with primary orthostatic tremor, together with a concomitant 6–8-Hz arm tremor in some primary orthostatic tremor patients, it is still thought that there may be some overlap between the two conditions. Doubt has now been cast on even these two pieces of evidence. First, in a recent large survey of patients with orthostatic tremor, McManis and Sharbrough report that the familial association may be merely coincidental (McManis and Sharbrough, 1993). Secondly, the experiments of this study suggest that in primary orthostatic tremor the 8-Hz arm tremor is a subharmonic of a common 16-Hz tremor widespread throughout the body and therefore one does not need to invoke a second diagnosis of essential tremor in such subjects.

Primary orthostatic tremor is considered to be the peripheral manifestation of a central oscillation. Evidence for this stems from a number of sources.

(i) Single motor unit studies reveal that individual units often fire at 8 Hz while locked into a 16-Hz modulation (Deuschl *et al*., 1987). Thus, the 16-Hz oscillation is not an innate abnormal motoneuronal rhythm but the result of synchronizing of motor units by an external oscillation. In the present experiments, the synchronization was sometimes so strong that surface EMG records revealed very little activity at all between the large and obviously polyphasic EMG bursts. In other words, nearly all the motor units have been 'trapped' together by the 16-Hz rhythm.

(ii) A classic way of assessing if a peripheral modulation is central in origin is to determine if the phase of tremor can be reset by appropriate electrical peripheral nerve shocks. Such resetting does not occur in primary orthostatic tremor (Britton *et al*., 1992).

(iii) A linking between the oscillations in different muscles has been revealed by cross-correlation between single motor units (Britton *et al*., 1992). The present study shows that all the muscles involved in primary orthostatic tremor (and sometimes even those that appear quite inactive such as the deltoids during standing) share strong coherence and are therefore driven by the same oscillation. An oscillation able to drive a number of widely separated muscles in a coherent manner is likely to reside centrally. The only way a single peripheral oscillation could spread to widely separated parts of the body is by reafferent linkage via peripheral feedback loops between one motor neuron pool and another. This seems unlikely since (a) accelerometer recordings indicate a lack of 16-Hz tremor movement so that the afferents would not be carrying a modulation of that frequency and (b) peripheral loops would create relatively fixed time lags rather than lags that vary in a consistent manner for different subjects and different tasks.

(iv) Finally, functional imaging has shown a bilateral abnormal cerebellar activation during primary orthostatic tremor (Wills *et al*., 1994), suggesting cerebellar involvement in this condition, although this activity could represent the result of, rather than the origin of the tremor.

The common central oscillator driving the EMG modulations of many different muscles in primary orthostatic tremor contrasts with findings in normal subjects and serves to illustrate the very high consistency of phase relationships in primary orthostatic tremor compared with those found normally. This study shows that peak surface EMG frequencies in large arm and leg muscles during different postures are weak in normal subjects and lie in the range of 10–15 Hz. There is no coherence between any of these muscles, even between homologous muscles whose peak EMG frequencies tend to be very similar. If central oscillators play any role in the generation of these normal peak frequencies, their linkage must be insufficiently strong to be manifest in the periphery. Such findings can be compared with previous studies showing that, in normal subjects, coherence of EMG modulation frequencies is absent between widely separated small hand muscles (McAuley and Brown, 1995) and between the biceps muscles (Bruce and Ackerson, 1986), although significant coherence is found between neighbouring small hand muscles contracting together (Farmer *et al.*, 1993) and between respiratory muscles during breathing (Bruce and Ackerson, 1986). It is likely that when coherence does exist in normal subjects, it sometimes arises as a result of branched inputs to the motor neurons (Kirkwood *et al.*, 1982; Farmer *et al.*, 1993) or a low-level brainstem oscillator (Cohen, 1979). Such mechanisms cannot explain the coherence found in primary orthostatic tremor, where the coherence displays plasticity and is out of phase (i.e. fixed but non-zero phase difference).

The phase relation between different muscles and their task-specificity

Since primary orthostatic tremor clearly seems to be central in origin, the strength and regularity of its modulation of peripheral EMG activity provides a unique opportunity to study in detail how the oscillation modulates central pathways controlling different peripheral structures, and to study the relationship between the phases of the oscillation in these different pathways.

Previous studies on primary orthostatic tremor have commented on the relative timing of the bursts and some have suggested that it may have a stereotyped pattern (Thompson *et al.*, 1986; Deuschl *et al.*, 1987; Britton *et al*., 1992). However, this pattern has not been quantified. The present experiments employ analysis in the frequency domain to quantify the patterns for the first time.

The results show that the muscles do not contract together, yet the strong coherence indicates that the 'staggered' and seemingly random pattern of timings is fixed over a whole 2 min trial. Moreover, provided the subject repeats similar postures, the pattern remains similar over a whole experimental session lasting several hours. This is a remarkable observation when one considers that no phase pattern resetting has occurred over a period in which up to 200 000 cycles took place. However, when the nature of the posture changes, such as when crouching on all fours instead of standing up, the pattern dramatically changes to a new fixed relationship. The explanation of the time lags clearly does not lie in different motor conduction times (as determined by transcranial magnetic stimulation) to the different muscles (see Fig. 3), nor does it lie in different peripheral feedback loop delays, as already discussed. A variability in the time to reach recruitment thresholds for different motoneuronal or corticomotoneuronal pools is also an unlikely explanation as this would result in more variability over a 2 min trial and between different trials as well as between the pools of different muscles. To explain the observed results, such a mechanism would have to generate a consistent and fixed delay of up to the order of 30 ms between two muscles.

Nature of the central oscillation and the task-specific phase relations

The findings of this study argue against the presence of a single central oscillator that simply sends a pulsatile output directly through corticospinal pathways to the muscles. Instead, at some point in the pathway, tightly-controlled, task-specific and quite long-duration time or phase delays are incorporated. Three explanations for such a phenomenon present themselves.

(i) The condition itself could consist of abnormal neural circuits that, as well as producing the 16-Hz oscillation, incorporate different time delays. However, it seems highly unlikely that a pathological process, with no clinical deficit other than tremor, could result in numerous sets of abnormal circuits, each specific for a certain posture, that generate such a complex pattern of delays between impulses to the different muscles and at the same time allow all these postures to be adopted correctly. (The superadded disabling 16-Hz tremor simply prevents them from being maintained for very long.)

(ii) The incorporation of timing or phase delays into integrated motor commands for posture control may instead represent a normal phenomenon and in primary orthostatic tremor these postural commands somehow become modulated by a pathologically strong 16-Hz oscillator. The timing relationships thus become uncovered in this condition because the oscillation is so powerfully and widely manifest in peripheral muscle activity. The timing delays clearly have no direct meaning with regard to the mechanics of normal muscle action as they influence a modulating oscillation rather than time the onset of discrete movements and so are likely to be part of the control rather than the implementation of postural action. They could therefore reflect conduction delays resulting from the passage of signals through normal complex neural posture control networks in the brain or spinal cord. Different pathways in the network might take part in controlling different muscles in different postures. The pathways would be highly 'plastic' in nature and not necessarily have identical patterns of connection in different individuals since there could be an almost infinite number of possible network 'solutions' to the same postural task. Nevertheless, this plasticity would be capable of being very tightly controlled to result in a consistent timing of bursts over periods of minutes or even hours. Perhaps this could reflect the fact that, once a network 'solution' for control and maintenance of posture is achieved, it tends to be preserved. However, it is tempting to suggest that the strong linking of oscillations with specific phase lags represents some active process rather than an epiphenomenon related to signals happening to pass along different pathways through a neural network.

(iii) The fixed coupling between signals to different muscles and the variable but controlled phase relationships may be a mechanism for controlling all the muscles involved in posture as a single unit. Based upon studies of the time-locked and stereotypical performance of widely separated muscles engaged in complex reflex activity, it has already been suggested that such muscles groups are essentially controlled synergistically in this way (McCollum, 1993). There is evidence from olivocerebellar recordings in animals that coupling of muscle activity could be achieved by phase-locking of olivary neurons with a common superimposed synchronizing oscillation at 6–10 Hz (Welsh and Llinás, 1997). In addition, the pattern of phase-locking across these olivary units is found to be plastic and task-specific. It is therefore possible that the phase-locking of muscle oscillations seen in primary orthostatic tremor could reflect a similar physiological oscillatory control mechanism since the coherence between particular muscle oscillations can change and is entirely dependent on those muscles being involved in postural activity.

Clearly, if primary orthostatic tremor did indeed arise from an olivary oscillation, it would have to be distinct from those olivocerebellar oscillations thought to result in essential tremor. The latter are at the more normal 7–12 Hz frequency for such oscillations and do not display linking on a widespread scale between different limbs; nor is there the same degree of task-specificity. An interaction with peripheral mechanisms may also be important in the generation of essential tremor, while primary orthostatic tremor seems virtually independent of peripheral modulation of tremor. The pathological process resulting in primary orthostatic tremor could be an alteration in frequency or amplitude of olivary or other coupled central oscillations so that they become strongly manifest in the periphery. It is possibly relevant to note that the olivary synchronizations described by Welsh and Llinás are restricted by GABAergic inputs and that GABA-mediated drugs such as clonazepam are usually more effective than β-blockers or alcohol in alleviating the symptoms of primary orthostatic tremor (Welsh and Llinás, 1997) (see Table 1).

If the pathology of primary orthostatic tremor is indeed simply an uncovering of normal coupled oscillatory modulations, what would be the role of such oscillations? The functional grouping of motor commands by common oscillations has been referred to as 'binding' (Welsh and Llinás, 1997) and might enable signals belonging to a particular muscle synergy to be identified as belonging together. Rather than requiring separate neural pathways for every possible combination of multiple, perhaps simultaneously performed tasks, the groups of signals associated with different types of activity (e.g. voluntary or postural) may be identified by their common oscillations as well as by their synaptic connections. Taking this a stage further, if the same oscillation modulated all postural activity, the phase patterns revealed by primary orthostatic tremor could enable the unique identification of each posture even though they were processed through the same pathways with the same common modulation. The possibility that such a phase coding mechanism could exist as a general phenomenon in the CNS is supported by studies on rat hippocampal spatial memory cells (O'Keefe and Recce, 1993). The phase of regular firing

of such cells relative to that of background 7–12-Hz EEG activity is specific for the animal's spatial location and changes for different locations. Of course, evidence for binding and for phase coding must remain circumstantial without the demonstration of CNS processes that can identify common oscillations with consistent phase patterns and then implement motor activity on this basis.

In summary, this study supports previous findings indicating that the 16-Hz primary orthostatic tremor rhythm arises from a central oscillator. The fact that the peripheral manifestation of the oscillation in different muscles is so strong allows a quantitative analysis of the frequencies and phases of oscillation in the central outputs to different muscles. This analysis reveals a linkage between these oscillations with a complex and task-specific pattern of phase delays and suggests that these phase delays may reflect the activity of normally occurring neural networks or oscillators involved in postural control.

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