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RESEARCH ARTICLE

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Corticomuscular coherence in the 6–15 Hz band: is the cortex involved in the generation of physiologic tremor?

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Abstract Physiologic tremor (PT) consists of a peripheral mechanical oscillation at the limbs' resonance frequency and an independent central component in the 6–15 Hz band. This central component has mainly been attributed to spinal interneuronal systems or subcortical oscillators but more recently also to cortical rhythms. We recorded PT electromyographically and accelerometrically from different parts of the arm in parallel to epicortical recordings from grid electrodes covering the primary sensorimotor areas of the contralateral cortex in six epileptic patients. Previous bipolar electrical stimulation of the cortical electrodes resulted in a somatotopic map of the primary cortex underlying the grid. Spectral and cross-spectral analysis including coherence spectra between epicortical electrodes and EMG and the corresponding phase spectra were performed off-line. We found significant corticomuscular coherence in the 6–15 Hz range in four out of the six patients. This coherence was focal on the cortex and it was distributed somatotopically mainly within the primary motor area. The frequency band of the coherence mostly corresponding to the EMG frequency remained stable with added inertia, while the main accelerometric frequency was clearly reduced following the resonance frequency. The phase spectra between electrocorticogram (ECoG) and EMG showed a clear delay between cortex and muscle in two of the patients, which was compatible with conduction in fast pyramidal pathways. These findings indicate that the 6–15 Hz coherence between cortex and EMG reflects a corticomuscular transmission of the oscillation rather than peripheral feedback to the cortex. We conclude that cortical networks are involved in the generation of physiologic tremor.

Keywords Physiologic tremor · Motor cortex · Epicortical recordings · Corticomuscular coherence and phase · Central tremor generation

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Introduction

Physiologic tremor can be measured in any normal subject and has been shown to consist of two components. The limbs are driven at their resonant frequency by randomly firing motor units (Marshall and Walsh 1956; Elble and Randall 1978; Hömberg et al. 1987), and in parallel, a rhythmic central drive to the muscles in the 7–12 Hz range, which is independent of peripheral mechanics, has been described (Lippold 1970; Elble and Randall 1976; Marsden 1978). This latter component is of special interest as it shares some features with an 8–10 Hz rhythm that has been shown to govern slow voluntary movements in man (Vallbo and Wessberg 1993; Wessberg and Vallbo 1995, 1996) and with certain pathological tremors (Freund and Dietz 1978; Elble 1995). We have recently studied physiologic tremor in a large normal population and found that this central component is not restricted to the 7–12 Hz band. It often occurs at higher frequencies up to around 15 Hz, but never below 6 Hz (Raethjen et al. 2000b). We will therefore refer to the 6–15 Hz band in the following. This component has, so far, mainly been attributed to instabilities within the spinal circuitry (Allum et al. 1978; Elble and Koller 1990) or to subcortical oscillating structures like the inferior olive (Llinas and Pare 1995; Elble 1996). However, the recent finding of highly correlated muscle activation in the 6–15 Hz range between the left and

right side of the body in cases with abnormal bilateral corticospinal connections in congenital mirror movements (Köster et al. 1998) led to the hypothesis that the cortex might be involved in the generation of this tremor component. But all previous studies directly correlating the cortical signal as recorded by EEG or magnetoencephalography (MEG) with the peripheral EMG in normal subjects found significant corticomuscular coherence mainly in higher frequency bands of 15–30 Hz and 30–50 Hz (Conway et al. 1995; Baker et al. 1997; Mima and Hallett 1999; Brown 2000), and hardly ever in the range of PT (Marsden et al. 2000a, 2000b; Ohara et al. 2000).

In the present study we used epicortical recordings from grid electrodes in epileptic patients to increase the signal-to-noise ratio and correlated these data with concurrently recorded EMG from different muscles in a setting especially adapted for tremor analysis (Raethjen et al. 2000a). We demonstrate that there is a reproducibly significant coherence between the cortex and the peripheral signal in the 6–15 Hz range and that these coherencies are efferent in nature rather than reflecting mere feedback from the periphery, thus indicating that the motor cortex drives muscles in the frequency band of the central component of PT. Preliminary results have been presented in abstract form (Raethjen et al. 2000a).

Patients and methods

Patients

We analysed three female and three male patients with intractable focal epilepsy before undergoing surgery to remove an epileptic focus. The age of the patients ranged from 16 to 40 years. One of the patients had an anatomical abnormality in the area of the suspected focus that was visible in the prefrontal area on the cerebral MRI scan and resulted in a slight contralateral hemiparesis (patient 2 in Table 1). It was a very mild sign (MRC grade 4–5) and was only found in the careful neurological examination performed in all the patients, while the patient and her relatives reported normal use of the extremity in everyday life. In accordance with this history we did not find a marked reduction in dexterity or slowness of fast repetitive movements on examination. All the other patients had no clinical neurological signs or symptoms apart from their seizures. None of the patients had a history or family history of tremor. Prior to the presurgical diagnostic period, all antiepileptic drugs were withdrawn and a monotherapy with carbamazepine was initiated. The carbamazepine dose was reduced quickly until seizures occcurred regularly allowing ECoG recordings of epileptic activity for focus localization. Thus all patients were taking relatively low doses of carbamazepine at the time of the recordings. The patients had subdural epicortical grid electrodes implanted covering parts of the primary sensorimotor area of the cortex, but the epileptic focus as located in the epicortical recordings was distant from these primary areas in all patients. They gave informed consent and the study was approved by the ethics committee of the University of Bonn, where all the recordings were performed.

Electrostimulation of epicortical electrodes

The epicortical grids consisted of 8×8 electrodes. The distance between neighbouring electrodes was 1 cm. Before the tremor recordings the grid electrodes were stimulated using both synchronized subunits of the GRASS S-88 stimulator to generate bipolar charge-balanced biphasic pulses of 250 ms duration at frequencies of 10, 30 and 60 Hz and with amplitudes between 30 and 60 mV. The duration of these impulse-series ranged between 4 and 5 s. The contacts of the grid were stimulated pairwise in the anterior–posterior and the lateral–mesial direction on subsequent days. Sensory effects as reported by the patients and visible motor effects of the stimulations were protocolled thoroughly. This resulted in a topographical picture of the functional anatomy of the underlying cortical areas. As all grids covered at least the hand area, we found motor effects on electrical stimulation in the hand and fingers in all patients. In four patients we found a motor response of the whole arm and shoulder when stimulated more mesially. A typical example of a grid covering parts of the primary sensorimotor cortex is illustrated in Fig. 1 in a three-dimensional reconstruction of an MRI scan.

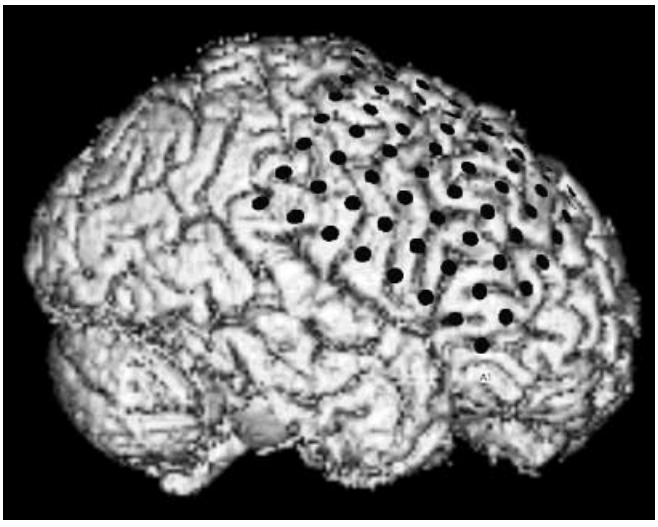

Fig. 1 Three-dimensional MRI reconstruction of the grid position on the cortex of patient 3 of Table 1. The grid location and orientation was similar in all analysed patients, covering the primary sensorimotor cortex at least partly

Data recording

All data were sampled at a rate of 520 Hz. The electrocorticogram (ECoG) was bandpass filtered between 0.53 and 160 Hz and treated as a monopolar recording with a distant reference and ground. The reference electrode was one of the grid electrodes that was far away from the primary cortical areas of interest and the epileptic focus. The results were consistent for different choices of that reference electrode. The same reference electrode was used for all recordings in one subject. The results obtained for Laplacian referencing (Hjorth 1975) also qualitatively agree with those from single electrode referencing. When referencing to the common average of all grid electrode signals, large differences in variance among the grid electrodes cause a spread of coherent activity from the electrodes with largest variance to other electrodes, rendering this scheme unsuitable for the present situation.

In parallel with the ECoG, bipolar surface EMG and accelerograms were recorded from those regions of the body that showed a motor response on cortical electrostimulation. Silver chloride electrodes were fixed over the muscle belly close to the motor points and uniaxial piezoelectric accelerometers were fixed on the corresponding parts of the body. The EMG was bandpass-filtered between 50 and 260 Hz on-line. High-pass filtering at 50 Hz is the standard demodulation procedure in tremor analysis, allowing analysis of the tremor burst modulation in the rectified EMG while cutting out the movement artefacts produced by the tremor excursions (Journée 1983). The accelerometer data were only low-

pass filtered at 260 Hz. In all patients finger (preferentially the first dorsal interosseus, FDI), hand (preferentially the extensor carpi ulnaris, ECU) and shoulder (preferentially the deltoid) muscles were recorded with the accelerometer fixed on the tip of the index finger, the dorsum of the hand and the dorsal forearm, respectively. Hand and arm tremor was recorded with the hand or arm extended against gravity with and without added weight (1000 g), which was fixed in the same place as the accelerometers. This also is the standard procedure in human tremor recordings (Elble and Koller 1990; Halliday et al. 1999). In the finger we recorded force tremor with the index finger pressed against the thumb at medium strength. As the accelerometry recorded from the tip of the index finger in this setting is difficult to interpret in terms of tremor, we only used it to control for superimposed voluntary movements and did not perform time-series analysis on these data. We did not control for the strength of contraction, it was relatively weak when the hand or arm was only extended against gravity and medium when weight was added. In one patient we also recorded the ECU and deltoid muscles simultaneously. The duration of each recording was between 40 and 60 s, each recording was repeated under the same conditions at least three times.

Data analysis

The raw data were inspected for artefacts and stationarity off-line, and only clearly stationary artefact-free data were used for further analysis. The EMG data were full-wave rectified. Autospectral and cross-spectral analysis between simultaneously recorded ECoG and EMG or accelerogram up to a frequency of 60 Hz was performed using the following procedure, which is described in detail elsewhere (Timmer et al. 1996).

Data were tapered with a Bartlett window to reduce leakage. The periodogram of the data was computed using an efficient non-radix-2 fast Fourier transform algorithm, thus avoiding the need for zero-padding. The auto- and cross-spectra were estimated by smoothing the periodogram and the cross-periodogram with a Bartlett window of width 1.0 Hz, yielding a spectral resolution of about 0.75 Hz. The coherence, a bounded measure of linear correlation, is defined as the absolute value of the cross-spectrum normalized by the square root of the product of the autospectra of the two processes under study. It is estimated from the measured data as described in detail in Timmer et al. (1998a). It can be shown that the coherence is equal to 1 whenever one process is a linear function of the other process, and equal to 0 in the case of linear independence (Brockwell and Davis 1991). Thus, it can be interpreted as a measure of linear predictability. Its statistical significance was examined by referring to the critical value for the null hypothesis of zero coherency. The calculation of the level of significance was performed according to the descriptions in Brillinger (1981). When testing for significant coherence within a band of frequencies, the Bonferroni correction was applied. A significant corticomuscular coherence in one frequency band was only interpreted as an indication of corticomuscular coupling when it could be reproduced in at least two of the recordings of one muscle in the same patient.

The phase spectrum, defined as the argument of the cross-spectrum, may be used to assess the timing relation between the processes. If the coherence between two signals is due to the fact that one process is a lagged version of the other process, then the phase spectrum follows a straight line with the delay given by the slope of the line (Timmer et al. 1998a). We only calculated phase spectra for patients and muscles with a clearly reproducibly significant coherence as described above. As the standard deviation of the phase estimate is proportional to the inverse of the coherence at a given frequency, a wide region of significant coherence is needed in order to reliably establish the existence of a linear phase curve. In those cases in which significant coherence was reproducibly found in a frequency band of at least 7.5 Hz width, corresponding to ten independent estimates of coherence and phase, a straight line could be safely fitted to the phase curve and the delay could be estimated reliably. However, it was also often possible to distinguish between a positive (cortex leads muscle) or negative (cortex lags muscle) delay in cases with narrower bands of significant coherence. A weighted least-squares fit was used; the weights assigned were proportional to the inverse of the standard deviation of the phase estimate at every point. The delay estimate for a single measurement (slope of the fitted straight line) is asymptotically normally distributed with a certain standard deviation. The goodness-of-fit of the data to the linear model was evaluated (Press et al. 1992). The delays across all reproduced measurements of the same muscle and patient were pooled by calculating a weighted average. The estimated delays with small standard deviations were weighted stronger than those with high standard deviations. The standard deviation of this result was calculated according to error propagation.

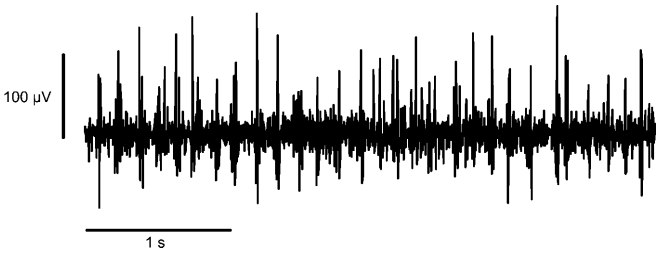

Fig. 2 Sample EMG recorded from the forearm extensors (preferentially ECU) in patient 3 without load. Rhythmic burst activity can be seen at around 7 Hz

Table 1 Summary of the results in all six patients. *X* 6–15 Hz band, *Y* 15–30 Hz band (*FDI* first dorsal interosseus muscle, *ECU* extensor carpi ulnaris)

	Reproducible coherence		
	FDI	ECU	Deltoid
Patient 1	X[a]	X	X
Patient 2		X	X
Patient 3	X	X	X
Patient 4			
Patient 5	X	X	
Patient 6	Y	Y	

[a] The X or Y indicates a significant coherence between a circumscribed cortical area and the respective muscle that was reproducible in at least two subsequent recordings of 40–60 s duration. As we performed surface-EMG recordings, we recorded from a group of muscles at the forearm with preference of the muscle indicated

Results

Significant corticomuscular coherence in the 6–15 Hz band

The EMG and accelerometer spectra of all patients and muscles showed significant peaks in the 6 to 15 Hz range in at least one recording. Taking all recordings in all patients together, we found a significant peak in 65–75% of all EMG spectra. A sample EMG record of a forearm extensor (ECU) with a clearly rhythmic burst activity is displayed in Fig. 2. Even in those spectra with no significant peak, the power in the 6–15 Hz range mostly ex-

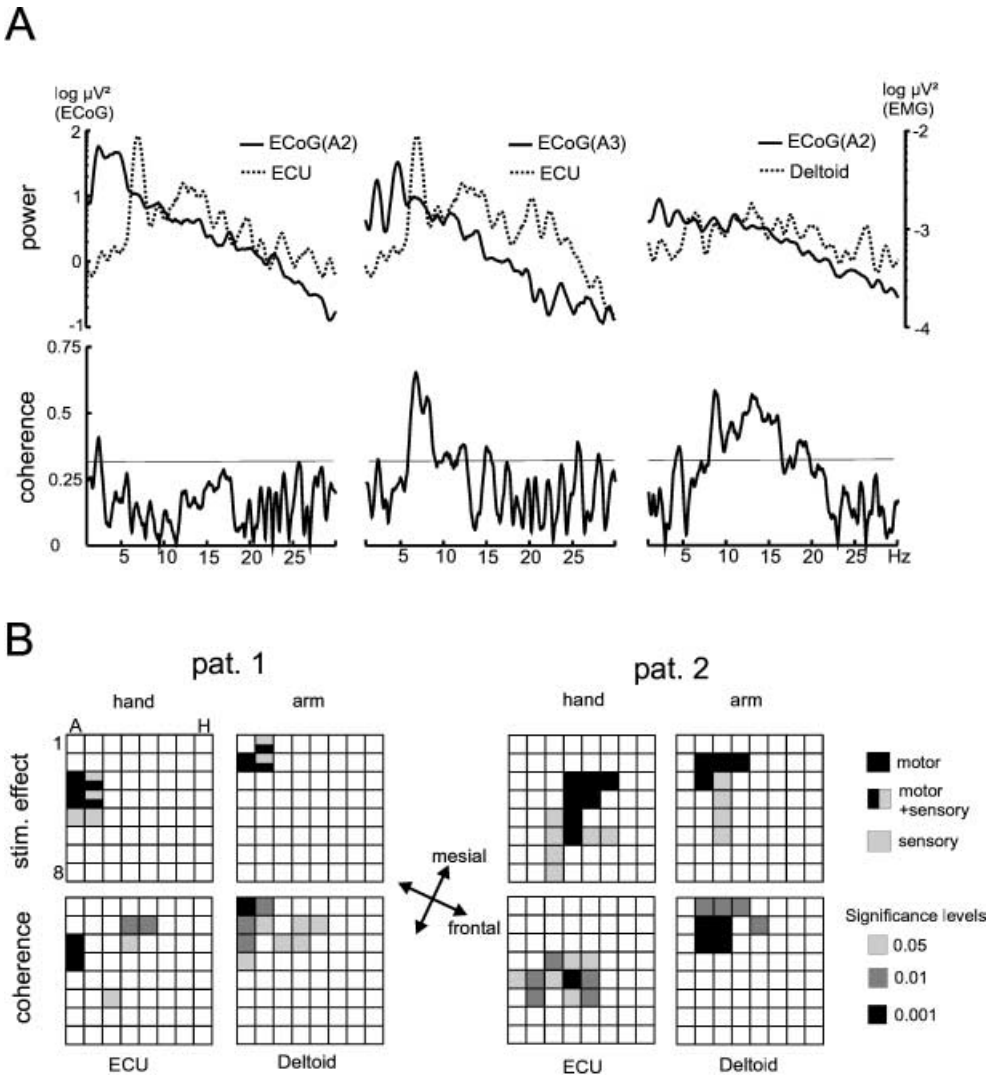

Fig. 3A, B Significant corticomuscular coherence in the 6–15 Hz band, focal and somatotopically organized mainly within the motor cortex: **A** Examples of ECoG and EMG spectra (*top row*) and the respective corticomuscular coherence spectra (*bottom row*). The number of the ECoG electrodes corresponds to the labels of the 8×8 matrix shown for patient 1 in Fig. 3B. The first two columns display the autospectra and the coherence spectra between the EMG of the forearm extensors (preferentially the ECU) and two neighbouring epicortical electrodes. The horizontal lines in the coherence spectra indicate the 5% level of significance. The reference electrode used in this patient was located at H8 with location in relation to the relevant cortical areas as seen in Fig. 3B. Although the ECoG spectra look similar for both electrodes, there is significant coherence only for one of the two cortical sites. The frequency band of significant coherence extends from 6–15 Hz with the main peak coinciding with the tremor peak as seen in the ECU spectrum (*broken line*) at about 7 Hz. There is no corresponding peak in the ECoG spectrum, which has its main power in the delta and theta bands. The power spectra and the coherence spectrum between ECoG and deltoid muscle are displayed (*third column*), this is an example of a significant 6–15 Hz corticomuscular coherence without a clear tremor peak. There were other recordings of the deltoid in this and other patients, however, which also showed a significant tremor peak in the EMG spectrum. The ECoG electrode that was coherent to the deltoid muscle (A2) was not coherent to the ECU (*first column*), illustrating how focal the corticomuscular coherence was on the epicortical grid. The small peak in the leftmost coherence spectrum at about 2 Hz barely rose above the 5% level of significance with only one point of the coherence spectrum, it was not reproducible in repeated recordings and it cannot be interpreted as an indication of corticomuscular coupling at this frequency. It most likely represents one of the expected 5% errors of first type. **B** Topographical distribution of the corticomuscular coherence in relation to the effects of the electrical cortical stimulation. The grid is displayed schematically for two patients as an 8×8 matrix. Anatomical directions are given in the middle (*arrow cross*). The results from two patients are shown: the cortical areas that gave rise to a motor or sensory or combined response in the contralateral hand or arm on bipolar electrical stimulation (*upper row*), and the reproducibly coherent electrodes with the respective muscle (*lower row*). The minimal level of significance of the main coherence peak in the 6–15 Hz range across at least two recordings are gray-scale coded. The area of reproducible corticomuscular coherence corresponds well with the stimulation effect: the more proximal the muscle, the further mesial are its cortical representation and the area of reproducible coherence. The cortical electrodes, which are reproducibly coherent, lie preferentially within the motor representation of the respective part of the arm, although there is considerable overlap between the sensory and the motor areas

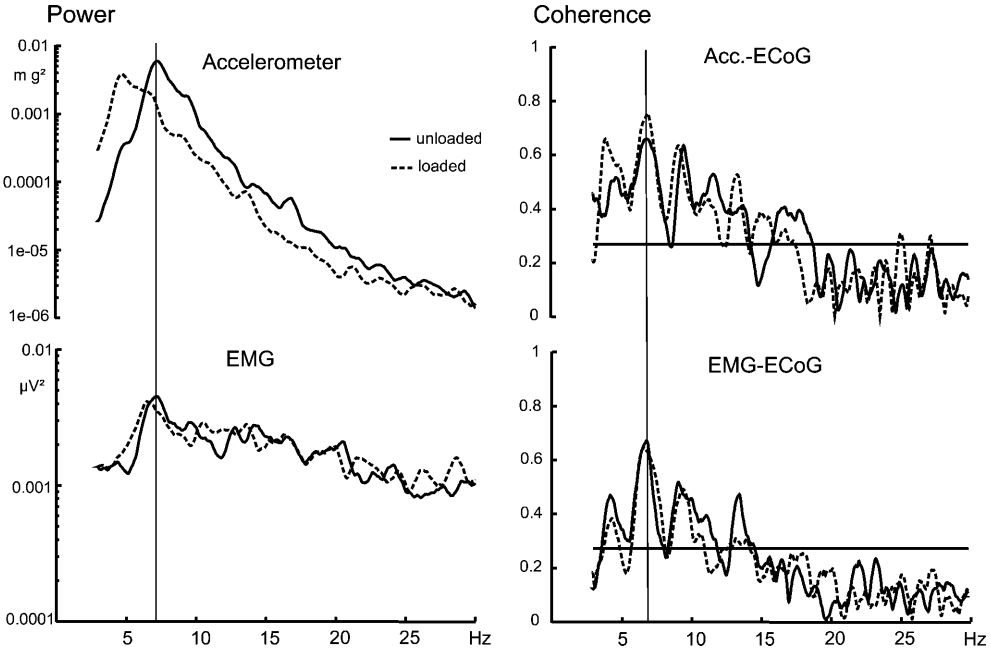

Fig. 4 Coherent frequency band does not depend on peripheral mechanics. The accelerometer and EMG spectra from the forearm extensors (preferentially the ECU, *left*) and the respective ECoG–EMG coherence spectra (*right*) are displayed. The spectra of recordings with and without weight are superimposed. While the main accelerometer frequency of the hand tremor drops considerably under a weight load of 1000 g, the frequency of the forearm extensors (ECU) and the frequency of the main coherence peak remain constant at about 7 Hz. This finding was well reproducible in different recordings and patients

ceeded the spectral power in other frequency bands. All patients showed a concentration of the ECoG power in the 2–10 Hz range with a continuous decline of spectral power towards higher frequencies, sometimes mounting to lower-frequency peaks in the ECoG spectra (Fig. 3A). In some patients there was an additional peak around 20 Hz.

In four patients there was a significant well-reproducible (in at least two recordings under the same conditions) coherence between the ECoG and the EMG of the hand extensor muscle (ECU) in the 6–15 Hz range (Table 1). There was also a reproducibly significant coherence between ECoG and a small finger muscle (FDI) or a shoulder muscle (deltoid) in two of these patients within the same frequency band. The frequency of the maximal coherence was interindividually variable, but coincided with the respective peak frequency of the EMG in the majority of the recordings (Fig. 3A). We also found the 6–15 Hz corticomuscular coherence in some of the recordings without a significant peak in the EMG spectrum (Fig. 3A, right). All patients occasionally also showed a higher frequency corticomuscular coherence in the 15–30 Hz band, but this coherence was mostly weaker and not as well reproducible. In only one patient did we find the only reproducibly significant coherence in the 15–30 Hz range. In another patient there was no reproducible significant corticomuscular coherence at all (Table 1). Whenever we found a corticomuscular coherence, there was a significant coherence between the accelerogram and the ECoG as well (see Fig. 4), except for the FDI force tremor, where we did not include the accelerogram in the analysis. The corticomuscular coherence was restricted to well-defined small cortical areas. Figure 3A shows a significant coherence between ECU and the ECoG only for one of two displayed epicortical electrodes, although they were next to each other on the cortex.

6–15 Hz corticomuscular coherence follows the somatotopy of the motor cortex

The detailed protocol of the electrostimulation allowed a good estimate of the functional cortical anatomy, especially with regard to the different somatotopic motor areas of the primary motor cortex. The functional cortical anatomy could then be compared to the strengths of coherence between the ECoG of each epicortical electrode and the tremor in different limbs. As illustrated in Fig. 3B, for two of the patients the corticomuscular coherence was focused within the cortical representation of the part of the limb under study. The exact grid position on the cortex as reconstructed from three-dimensional MRI data was shown for the first of the two patients in Fig. 1. The schematic representations of the grid electrodes in the 8×8 matrices in Fig. 3B were aligned according to the anterior–posterior and lateral–mesial directions on the cortex. The upper matrices display the motor and sensory effects of the cortical stimulation, whereas the lower ones indicate the region of a reproducibly significant corticomuscular coherence with the respective muscle. The minimal level of significance across at least two recordings under the same condition in the 6–15 Hz band is gray-scale coded for each cortical electrode. The coherence matrices clearly show that corticomuscular coherence is a rather focal phenomenon that shifts when the muscle under study changes from a hand (ECU) to an arm muscle (deltoid). When comparing the focus of the corticomuscular coherence with the focus of sensorimotor stimulation effects in the respective part of the upper extremity, this is in good accordance with a somatotopic organization of the coherence. Although there is some overlap between the two foci, the main coherence between ECoG and the deltoid EMG is found in the (upper) arm area of the primary motor cor-

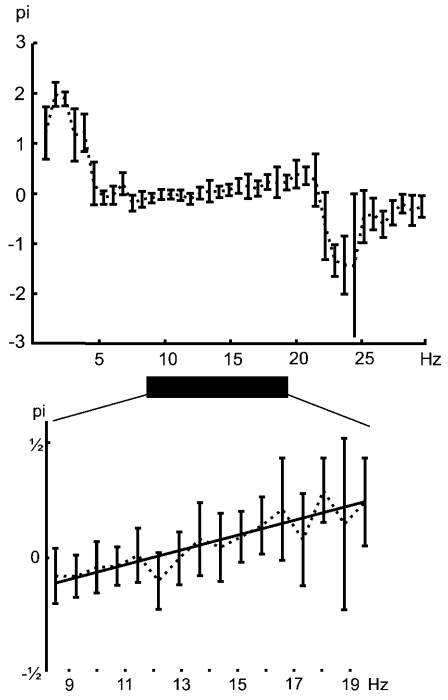

Fig. 5 Phase spectra show a corticomuscular delay. Phase spectrum between the deltoid muscle and a coherent epicortical electrode. The phase spectrum between 0 and 30 Hz (*upper trace*) with the estimated phase curve (*dotted line*) and the independent values representing ±2 standard deviations (*error bars*) are plotted. The frequency band of significant corticomuscular coherence can be seen by the relatively straight course of the phase curve and the small standard deviations in the 8.5 to 19.5 Hz range (*broad bar below the abscissa of the upper diagram*). The significant coherence sometimes extended up to frequencies slightly above 15 Hz, as shown here. But this was not reproducible and it always remained below 20 Hz. Therefore this did not indicate significant coupling in the 15–30 Hz band. The magnification of the phase spectrum in this frequency band (*lower trace*), which is well fitted by a straight line, is also shown. The corticomuscular delay can be calculated from the slope of this line. In this example there was a delay of 16 (±6) ms, which is in keeping with a transmission in fast pyramidal pathways

tex, whereas this coherence shifts into the hand area when recording from the ECU muscle. There seems to be some preference of the motor cortex, but there is also coherence in the primary sensory areas. Qualitatively identical results were obtained in the three other patients exhibiting corticomuscular coherence.

Frequency of coherence remains constant when resonant frequency is lowered by load

While the tremor frequency as recorded by accelerometry was reduced by more than 1 Hz under additional weight, the main coherence peak together with the corresponding EMG peaks remained stable at the same frequency. This was seen clearly for the accelerometer spectrum of the hand and the EMG of the hand extensors (ECU), as shown in a representative example in Fig. 4. The accelerometer frequency drops from the range 7–8 Hz to below 5 Hz, whereas the EMG peak frequency, the frequency of the maximal corticomusular coherence and the coherence between accelerogram and ECoG all remain stable at 7–8 Hz. Similar results were found in the other patients. The coherence peaks remained stable irrespective of the arm posture and added inertia.

Phase spectra show a corticomuscular delay

In two of the six patients we were able to estimate the exact positive time delays between the cortical and EMG signal in the range 6–15 Hz. These delays were well reproducible in most of the single recordings, and they were clearly significant in the pooled estimates of all reproductions under the same recording conditions. In one of these cases we found significant corticomuscular delays to the deltoid (mean: 16.5, two standard deviations: ±3.7 ms), ECU (19.2±9.4 ms) and FDI (17.0±5.6 ms) muscles, in the second patient it could be reliably estimated only to the FDI (22.2±6.6 ms). An example of a phase spectrum between cortex and the deltoid muscle in patient 3 of Table 1 indicating a corticomuscular delay is displayed in Fig. 5. The delay in this case was 16.0±6 ms. In the remaining two patients the frequency band of significant corticomuscular coherence was too narrow to estimate the exact delay time, however, the coherence was broad enough to indicate a lag of the EMG activity behind the ECoG signal (see Patients and methods).

Discussion

In the present study we consistently demonstrated significant coherence between the epicortically recorded signal and the peripheral EMG or accelerogram in the 6–15 Hz band. This low-frequency corticomuscular coherence was shown for the first time to follow the physiological somatotopy of the motor cortex similar to the 15–30 Hz component (Salenius et al. 1997). The frequency of significant coherence remained unchanged under additional inertial load, excluding peripheral feedback as the main mechanism of the 6–15 Hz corticomuscular coherence. On the contrary, we were able to show a clear corticomusular delay for the low-frequency component that is consistent with transmission via fast corticospinal pathways. We therefore conclude that the cortex is involved in the generation of physiological 6–15 Hz oscillations in the periphery and that this mechanism may well be related to the central component of PT.

Several possible mechanisms could be responsible for the coherence between the ECoG and the EMG signal in the periphery. Given that the main component of physiologic peripheral oscillations (physiologic tremor, PT) is mechanically resonant in nature (Hömberg et al. 1986; Raethjen et al. 2000b), the rhythmic sensory feedback could be the basis of a musculo-cortical coupling in the 6–15 Hz range. We tested for this possibility by system-

atically changing the resonant frequency of the hand by added inertia. This loading significantly decreased the main accelerometric frequency, confirming mechanical resonance as main cause of PT in our patients. The frequency band of significant corticomuscular coherence, however, remained perfectly constant together with the main EMG frequency, ruling out pure sensory feedback from the mechanical oscillations of the trembling hand. The lack of change in the coherence spectra definitely rules out even a minor reflex activation of the muscles by the mechanical tremor that may not be revealed by the EMG power spectra (Timmer 1998b), but may in turn lead to the corticomuscular coherence.

However, this result could still be explained by peripheral feedback from rhythmic muscle activity driven by a subcortical neuronal oscillator, for example, the inferior olivary nucleus (Llinas and Pare 1995), not directly involving the cortex. The most convincing method to distinguish between afferent and efferent coupling between cortex and periphery is to estimate the delays between the two signals from the phase spectrum. The delay is given by the slope of a straight line fitted to the phase curves in the frequency band of significant coherence. This method only yields clear results when this frequency band is broad enough for a reliable fit (Hamon and Hannan 1974; Timmer et al. 1998a; Hellwig et al. 2000). In our data pool, this method could be used to calculate a reliable delay time between cortex and muscle in two of the patients. The estimated positive corticomuscular delays between 16 and 22 ms are in keeping with a transmission via fast pyramidal pathways. In two other patients the phase spectra also indicated a clearly positive delay, that is, a lag between cortex and muscle, but the band of significant coherence was too narrow to calculate the exact delay time. Our findings therefore point to a cortical rhythmic drive and certainly exclude a mere rhythmic feedback activation of the cortex. The origin of this rhythmic activity could either lie in the cortex itself or originate from subcortical structures. It cannot be ruled out completely that a subcortically generated rhythm is transmitted to the peripheral muscles and the cortex in parallel. From a physiological point of view, however, it is very unlikely that the difference in delays matches exactly with the transmission time through fast corticospinal pathways. If the oscillation in the 6–15 Hz band is generated in subcortical systems, it seems far more plausible that these subcortical structures form an oscillating loop with the cortex as the principal and final output stage to the spinal cord, as has been proposed recently for pathological tremors (Plenz and Kital 1999; Deuschl et al. 2000).

Thus, although there are a number of ways in which such a corticomuscular coherence could emerge, our data make a corticomuscular transmission of a 6–15 Hz rhythm the most likely explanation, no matter whether this is generated in the cortex itself or in a loop involving subcortical structures.

But is this corticomuscular coherence related to the central component of physiologic tremor? The frequency band is very compatible with this tremor component. However, in a relatively small proportion of recordings (~30%) there was no clear indication of a central peak in the EMG spectra, despite a strong corticomuscular coherence in the 6–15 Hz band. This lack of an unequivocal association between the lower-frequency corticomuscular coherence and a central tremor peak could be interpreted in two ways. Either the corticomuscular coherence found in our study is a physiological phenomenon independent from physiological tremor, or there is rhythmic EMG activity also in recordings without a significant peak that is concealed by observational noise, which can become very strong in EMG recordings (Timmer et al. 1998a). In fact, one of the advantages of the coherence function is its ability to detect such hidden oscillations in two signals when they are linearly correlated (Brockwell and Davis 1991). The high proportion of an EMG synchronisation in the 6–15 Hz range occurring in at least one muscle in every patient and in about 70% of all recordings in our patient population indicates that the central component of PT was enhanced in our patients as it is found in no more than 20–30% of the recordings in a large normal population (Raethjen et al. 2000b). The stressful situation being examined in the lab with an implanted epicortical grid is one possible explanation, the withdrawal of antiepileptic drugs that is routine in invasive epileptologic procedures of this type might be another. Thus the circumscribed frequency band of corticomuscular coherence in the frequency band of the central component of PT, the well-recognized potency of the coherence function to detect hidden but linearly correlated oscillations and the clear indication of an enhancement of the central PT in our patients are strong arguments for an association of the present findings with the 6–15 Hz central component of PT.

Most previous studies dealing with corticomuscular coherence in the physiologic situation have used scalp EEG or MEG and mostly found coherent activity only in the 15–30 Hz range (Conway et al. 1995; Halliday et al. 1998; Mima and Hallett 1999; Brown 2000) or in the 35–60 Hz band for strong contractions (Brown et al. 1998), some of which found a strong influence of the motor task on this high-frequency coherence (Baker et al. 1997; Kilner et al. 1999). However, some authors already speculated on a possible role of the cortex also in the generation of the 6–15 Hz central component of physiologic tremor (Conway et al. 1995; Baker et al. 1997; Farmer 1998; Gross et al. 2000), which is often predominant in peripheral muscle recordings during weak isometric contractions (Freund 1983; McAuley et al. 1997). However, a recent study clearly showed that the motor units of small finger muscles fire in a synchronized fashion in both frequency bands in parallel, independent of added load to the finger (Halliday et al. 1999). In the present study we also found corticomuscular coherence in the 15–30 Hz range, which was the predominant coherence in one of the patients for the distal muscles. However, in the majority of our patients, the 15–30 Hz coherence was much weaker and not as well reproducible. There may be several reasons for the predominance of lower-frequency (6–15 Hz) coherence in

our patients. First, in contrast to all other studies, we used different recording conditions with unsupported extremities that were especially adapted for tremor analysis. Second, we did not examine healthy subjects, as all of our patients were epileptics. Although we did not analyse recordings in which we found any epileptic activity in the ECoG, we cannot rule out completely that the interictal brain activity is also more prone to show low-frequency coupling with the periphery. All patients were on low doses of carbamazepine at the time of the recordings, which has an effect on cortical excitability and can produce ataxia as a side-effect. Although none of our patients suffered from any carbamazepine side-effects, we cannot exclude an influence of this medication on our results. There were no indications of any other neurological abnormalities, except in one patient in whom we found a very mild hemiparesis (MRC grade 4–5) on the side of the muscle recordings, which did not interfere with dextrous and fast movement execution (see Patients and methods). As the strength of the coherence, the frequency band and the somatotopic organization all corresponded well to the results in the other three patients, this mild sign obviously did not have a significant influence on the corticomuscular coupling in the 6–15 Hz band. Finally, we used epicortical recordings with signal-to-noise ratios several orders of magnitude higher than scalp EEG and MEG. There is one recent study also using epicortical recordings in epileptics without any signs of movement disorders that also demonstrated consistent corticomuscular coherence in the low-frequency (around 8 Hz) range (Ohara et al. 2000). However, these authors did not measure the actual tremor activity. They recorded EMG only from one hand muscle and therefore could not look for somatotopy. As they only used cross-correlograms to analyse the timing relation between cortex and muscle, they could not reliably determine the direction of corticomuscular interaction. Interestingly, they could not only show coherence with the primary cortices but also with the SMA, indicating an involvement of higher-order cortical motor centres in the generation of the low-frequency rhythmicity in the periphery, which is most likely related to the central component of PT.

Taking together all the available data, there are three different frequency bands of corticomuscular coherence: at 6–15 Hz, 15–30 Hz and 35–60 Hz. However, the functions of these corticomuscular coherencies in motor physiology are not yet well understood. For the low-frequency corticomuscular coupling demonstrated in the present study, there are some important clues as to which functional role it may play in motor control. It has been shown that the electromyographic activation in slow voluntary movements is fractionated in small bursts with a frequency of 8–10 Hz (Vallbo and Wessberg 1993); this is considered a mechanism by which slow voluntary movements are controlled and graded by the CNS (Wessberg and Vallbo 1996). The corticomuscular coupling in this frequency range may well be related to this basic physiologic mechanism, but recent studies analysing the changes in epicortically recorded rhythms before and during movement performance seem to argue against the low-frequency coherence playing a role in the control of movements. It was shown that the low-frequency component (8–12 Hz) of cortical activity is clearly attenuated as soon as the movement begins (Toro et al. 1994; Aoki et al. 1999), whereas higher-frequency components (30–60 Hz) are enhanced (Aoki et al. 1999). However, the cortical rhythms were not correlated to the peripheral muscle activity in these studies and the movements tested were complex multijoint movements mostly involving visuomotor processing. The 8–12 Hz muscle activity was found in simple single-joint movements (Vallbo and Wessberg 1993) and in holding tasks (Freund 1983) similar to the one used in the present study. Thus, the low frequency corticomuscular coherence during simple motor tasks demonstrated in the present study and the changes in cortical alpha and gamma activity in relation to complex visuomotor control probably reflect different levels of movement planning and execution.

With regard to the probable connection to tremor physiology, the present results may also create a link with pathologic tremors: cortical involvement has been shown consistently for Parkinsonian tremor (Volkmann et al. 1996; Hellwig et al. 2000). In case of Essential tremor this is still a matter of debate. While Halliday et al. (2000) did not find corticomuscular coupling at the tremor frequency using MEG techniques, Hellwig et al. (2001) found a clear coherence between EEG and the peripheral tremor rhythm. The fact that a motor cortex-driven tremor is present in the physiological situation already might be an indication of the same central loops oscillating in PT and these common pathological tremors. The transition from physiologic to pathologic tremors may, indeed, be a mere enhancement of these central oscillations rather than a formation of new oscillators or oscillatory circuits (Freund and Dietz 1978; Elble 1986, 1995; Deuschl et al. 2001).

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References

Allum JH, Dietz V, Freund HJ (1978) Neuronal mechanisms underlying physiological tremor. J Neurophysiol 41:557–571

Aoki F, Fetz EE, Shupe L, Lettich E, Ojemann GA (1999) Increased gamma-range activity in human sensorimotor cortex during performance of visuomotor tasks. Clin Neurophysiol 110:524–537

Baker SN, Olivier E, Lemon RN (1997) Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. J Physiol (Lond) 501:225–241

Brillinger, DR (1981) Time series – data analysis and theory. Holden Day, San Francisco

Brockwell PJ, Davis RA (1991) Time series: theory and methods. Springer, New York

Brown P (2000) Cortical drives to human muscle: the Piper and related rhythms. Prog Neurobiol 60:97–108

Brown P, Salenius S, Rothwell JC, Hari R (1998) Cortical correlate of the Piper rhythm in humans. J Neurophysiol 80:2911–2917

Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, Rosenberg JR (1995) Synchronization between motor cor-

tex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol (Lond) 489:917–924
Deuschl G, Raethjen J, Baron R, Lindemann M, Wilms H, Krack P (2000) The pathophysiology of Parkinsonian tremor: a review. J Neurol 247:V/33–V/48
Deuschl G, Raethjen J, Lindemann M, Krack P (2001) The pathophysiology of tremor. Muscle Nerve 24:716–735
Elble RJ (1986) Physiologic and essential tremor. Neurol 36:225–231
Elble RJ (1995) Mechanisms of physiological tremor and relationship to essential tremor. In: Findley LJ, Koller WC (eds) Handbook of tremor disorders. Dekker, New York, pp 51–62
Elble RJ (1996) Central mechanisms of tremor. J Clin Neurophysiol 13:133–144
Elble RJ, Koller WC (1990) Tremor. Johns Hopkins University Press, Baltimore
Elble RJ, Randall JE (1976) Motor-unit activity responsible for 8- to 12-Hz component of human physiological finger tremor. J Neurophysiol 39:370–383
Elble RJ, Randall JE (1978) Mechanistic components of normal hand tremor. Electroencephal Clin Neurophysiol 44:72–82
Farmer SF (1998) Rhythmicity, synchronization and binding in human and primate motor systems. J Physiol (Lond) 509:3–14
Freund HJ (1983) Motor unit and muscle activity in voluntary motor control. Physiol Rev 63:387–436
Freund HJ, Dietz V (1978) The relationship between physiological and pathological tremor. In: Desmedt JE (ed) Progress in clinical neurophysiology. Karger, Basel, pp 66–89
Gross J, Tass PA, Salenius S, Hari R, Freund H-J, Schnitzler A (2000) Cortico-muscular synchronization during isometric muscle contraction in humans as revealed by magnetoencephalography. J Physiol (Lond) 527:623–631
Halliday DM, Conway BA, Farmer SF, Rosenberg JR (1998) Using electroencephalography to study functional coupling between cortical activity and electromyograms during voluntary contractions in humans. Neurosci Lett 241:5–8
Halliday DM, Conway BA, Farmer SF, Rosenberg JR (1999) Load-independent contributions from motor-unit synchronization to human physiological tremor. J Neurophysiol 82:664–675
Halliday DM, Conway BA, Farmer SF, Shahani U, Russell AJC, Rosenberg JR (2000) Coherence between low-frequency activation of the motor cortex and tremor in patients with essential tremor. Lancet 355:1149–1153
Hamon BV, Hannan EJ (1974) Spectral estimation of time delay for dispersive and nondispersive systems. Appl Statist 23:134–142
Hellwig B, Häussler S, Lauk M, Köster B, Guschlbauer B, Kristeva-Feige R, Timmer J, Lücking CH (2000) Tremor-correlated cortical activity detected by electroencephalography. Clin Neurophysiol 111:806–809
Hellwig B, Häußler S, Schelter B, Lauk M, Guschlbauer B, Timmer J, Lücking CH (2001) Tremor-correlated cortical activity in essential tremor. Lancet 357:519–523
Hjorth B (1975) An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephal Clin Neurophysiol 39:526–530
Hömberg V, Hefter H, Reiners K, Freund HJ (1987) Differential effects of changes in mechanical limb properties on physiological and pathological tremor. J Neurol Neurosurg Psychiatry 50:568–579
Hömberg V, Reiners K, Hefter H, Freund HJ (1986) The muscle activity spectrum: spectral analysis of muscle force as an estimator of overall motor unit activity. Electroencephal Clin Neurophysiol 63:209–222
Journée HL (1983) Demodulation of amplitude modulated noise: a mathematical evaluation of a demodulator for pathological tremor EMGs. IEEE Trans Biomed Eng 30:304–308
Kilner JM, Baker SN, Salenius S, Jousmaki V, Hari R, Lemon RN (1999) Task-dependent modulation of 15–30 Hz coherence between rectified EMGs from human hand and forearm muscles. J Physiol (Lond) 516:559–570
Köster B, Lauk M, Timmer J, Winter T, Guschlbauer B, Glocker FX, Danek A, Deuschl G, Lücking CH (1998) Central mechanisms in human enhanced physiological tremor. Neurosci Lett 241:135–138
Lippold OC (1970) Oscillation in the stretch reflex arc and the origin of the rhythmical, 8–12 C–S component of physiological tremor. J Physiol (Lond) 206:359–382
Llinas R, Pare D (1995) Role of intrinsic neuronal oscillations and network ensembles in the genesis of normal and pathologocal tremors. In: Findley LJ, Koller WC (eds) Handbook of tremor disorders. Dekker, New York, pp 7–36
Marsden CD (1978) The mechanisms of physiological tremor and their significance for pathological tremors. In: Desmedt JE (ed) Progress in clinical neurophysiology. Karger, Basel, pp 1–16
Marsden JF, Ashby P, Rothwell JC, Brown P (2000a) Phase relationships between cortical and muscle oscillations in cortical myoclonus: electrocorticographic assessment in a single case. Clin Neurophysiol 111:2170–2174
Marsden JF, Werhahn KJ, Ashby P, Rothwell J, Noachtar S, Brown P (2000b) Organization of cortical activities related to movement in humans. J Neurosci 20:2307–2314
Marshall J, Walsh EG (1956) Physiological tremor. J Neurol Neurosurg Psychiatry 19:260–267
McAuley JH, Rothwell JC, Marsden CD (1997) Frequency peaks of tremor, muscle vibration and electromyographic activity at 10 Hz, 20 Hz and 40 Hz during human finger muscle contraction may reflect rhythmicities of central neural firing. Exp Brain Res 114:525–541
Mima T, Hallett M (1999) Corticomuscular coherence: a review. J Clin Neurophysiol 16:501–511
Ohara S, Nagamine T, Ikeda A, Kunieda T, Matsumoto R, Taki W, Hashimoto N, Baba K, Mihara T, Salenius S, Shibasaki H (2000) Electrocorticogram-electromyogram coherence during isometric contraction of hand muscle in human. Clin Neurophysiol 111:2014–2024
Plenz D, Kital ST (1999) A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. Nature 400:677–682
Press WH, Teukolsky SA, Vetterling WT, Flannery BP (1992) Numerical recipes in C; the art of scientific computing. Cambridge University Press, Cambridge
Raethjen J, Lindemann M, Dümpelmann M, Stolze H, Wenzelburger R, Pfister G, Elger CE, Timmer J, Deuschl G (2000a) Cortical correlates of physiologic tremor. Mov Disord 15:P510
Raethjen J, Pawlas F, Lindemann M, Wenzelburger R, Deuschl G (2000b) Determinants of physiologic tremor in a large normal population. Clin Neurophysiol 111:1825–1837
Salenius S, Portin K, Kajola M, Salmelin R, Hari R (1997) Cortical control of human motoneuron firing during isometric contraction. J Neurophysiol 77:3401–3405
Timmer J, Lauk M, Deuschl G (1996) Quantitative analysis of tremor time series. Electroencephal Clin Neurophysiol 101:461–468
Timmer J, Lauk M, Pfleger W, Deuschl G (1998a) Cross-spectral analysis of physiological tremor and muscle activity. I. Theory and application to unsynchronized electromyogram. Biol Cybern 78:349–357
Timmer J, Lauk M, Pfleger W, Deuschl G (1998b) Cross-spectral analysis of physiological tremor and muscle activity. II. Application to synchronized electromyogram. Biol Cybern 78:359–368
Toro C, Cox C, Friehs G, Ojakangas C, Maxwell R, Gates JR, Gumnit RJ, Ebner TJ (1994) 8–12 Hz rhythmic oscillations in human motor cortex during two-dimensional arm movements: evidence for representation of kinematic parameters. Electroencephal Clin Neurophysiol 93:390–403
Vallbo AB, Wessberg J (1993) Organization of motor output in slow finger movements in man. J Physiol (Lond) 469:673–691
Volkmann J, Joliot M, Mogilner A, Ioannides AA, Lado F, Fazzini E, Ribary U, Llinas R (1996) Central motor loop oscillations in Parkinsonian resting tremor revealed by magnetoencephalography. Neurology 46:1359–1370
Wessberg J, Vallbo AB (1995) Coding of pulsatile motor output by human muscle afferents during slow finger movements. J Physiol (Lond) 485:271–282
Wessberg J, Vallbo AB (1996) Pulsatile motor output in human finger movements is not dependent on the stretch reflex. J Physiol (Lond) 493:895–908