



Review

A review of recent applications of cross-correlation methodologies to human motor unit recording

S.F. Farmer ^{a,b,*}, D.M. Halliday ^c, B.A. Conway ^d, J.A. Stephens ^e, J.R. Rosenberg ^c^a Department of Neurology, St Mary's Hospital, Praed Street, London W2 1NY, UK^b Department of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK^c Division of Neuroscience, Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK^d Bioengineering Unit, University of Strathclyde, Glasgow G4 0NW, UK^e Department of Physiology, University College and Middlesex Hospital School, London WC1E 6BT, UK

Abstract

This article reviews some recent applications of time and frequency domain cross-correlation techniques to human motor unit recording. These techniques may be used to examine the pre-synaptic mechanisms involved in control of motoneuron activity during on-going motor tasks in man without the need for imposed and artificial perturbations of the system. In this review we examine, through several examples, areas in which insights have been gained into the basic neurophysiological processes that bring about motoneuron firing in man and illustrate how these processes are affected by central nervous system pathology. We will demonstrate that synchronization and coherence may be revealed between human motor unit discharges and give examples that support the hypothesis that these phenomena are generated by activity in a focused common corticospinal input to spinal motoneurons. Disruption of central motor pathways due to diseases of the nervous system leads to pathophysiological alterations in the activity of these pre-synaptic motoneuron inputs that can be revealed by cross-correlation analysis of motor unit discharges. The significance of these studies and outstanding questions in this field are discussed © 1997 Elsevier Science B.V.

Keywords: Motor unit; Electromyogram; Synchronization; Cross-correlation analysis; Coherence analysis; Plasticity; Oscillation; Magnetoencephalogram

1. Introduction

Functional connections in the human motor system have been extensively examined through recordings of neurophysiological activity evoked by electrical, magnetic or reflex stimulation (see Rothwell, 1994 for review). In certain situations voluntarily initiated electromyographic (EMG) activity can be studied using different forms of cross-correlation analysis. The advantage of this approach is that it allows inferences to be made concerning the pre-synaptic control of motoneurons without the need for imposed perturbations. We define pre-synaptic control in man as the spatio-

temporal organisation of all motoneuron inputs, activity in which provides the pre-synaptic drive necessary to evoke motoneuron post-synaptic potentials and thus repetitive motoneuron discharge. This article will review some of the recent applications of cross-correlation techniques to human EMG recordings.

Traditionally it was believed that motor units in man fired independently of one another (Fulton and Liddell, 1925; Adrian and Bronk, 1929; Gordon and Holbourn, 1948; Bigland and Lippold, 1954; Taylor, 1962; Kranz and Baumgartner, 1974), with synchronization of motor unit discharges only occurring during powerful contractions (Piper, 1912; Adrian, 1947; Person and Kudina, 1968), during fatigue (Buchthal and Madsen, 1950; Person and Mishin, 1964), following training

* Corresponding author.

(Milner-Brown et al., 1975) or in disease (Hoefler and Putman, 1940, Buchtal and Honke, 1944; Buchtal and Madsen, 1950). However, these early studies were primarily based on visual inspection of the EMG. The application of cross-correlation analysis to human EMG recording demonstrated that motor unit synchronization may occur in healthy subjects during gentle isometric contraction (Dietz et al., 1976; Sears and Stagg, 1976; Dengler et al., 1984).

Early applications of cross-correlation analysis involved the recording of extracellular spike activity from invertebrate neurons in which synaptic interaction is mediated by large post-synaptic potentials (PSPs) (Moore et al., 1970). The times of occurrence of spikes from two neurons were treated as stochastic point processes and used to construct a histogram in which the times of the reference spikes, defined as time zero, were correlated with those of another spike train, the response. In the absence of synaptic interaction, the neuronal discharges are temporally unrelated and the histogram flat. The appearance of peaks or troughs in the histogram indicate a raising or lowering of response neuron firing probability brought about either by direct synaptic communication between the neurons or through the influence of a pre-synaptic input that is common to the neurons. These early studies identified primary and secondary effects in the cross-correlogram. In the situation where one of the neurons acts as an excitatory input to the other, thus modulating its firing, a peak of increased firing probability appears at a delay corresponding to the time taken for the discharges of the first neuron to influence the second and for this to be recorded. The time course of this primary effect reflects that of the change in firing probability brought about by the post-synaptic potentials. In the case where recordings are made from a pair of neurons that share a common pre-synaptic input, the primary effect is recognised as a peak of increased firing probability centred around time zero. In these early studies, secondary effects were also recognised in the histograms which often appeared as periodicities mapping to either side of time zero. In the case of common pre-synaptic inputs these effects may represent periodic firing of the two output neurons, in which case the time course of the secondary features is similar to that of the output neurons' autocorrelation functions. Alternatively, secondary effects may represent periodic firing of common input neurons, in which case the displacement of the secondary peaks from time zero reflect the autocorrelation functions of the common pre-synaptic inputs (Moore et al., 1970).

Initial studies using cross-correlation analysis of motoneuron activity in mammals paid particular attention to the cat respiratory system (Sears and Stagg, 1976; Kirkwood and Sears, 1978). These studies elucidated

properties of features in the cross-correlogram and their relation both to the time course of common input to motoneurons and its spatial distribution. The importance of these animal studies was that they enabled researchers to interpret cross-correlogram peaks at around time zero in basic neurophysiological terms. This led to the technique's widespread application to studies of human motor control in both health and disease. The following examples illustrate some of the ways in which different types of time and frequency domain correlation analysis have been used in order to gain new insights into the control of motoneuron activity in man.

2. The time course of human motor unit synchronization

Sears and Stagg (1976) described the phenomena of short-term synchronization which was detected as a central peak in the cross-correlation histogram of duration ± 3 ms. This, they reasoned, could occur due to the branching of last order pre-synaptic inputs in order to deliver near simultaneous EPSPs to the motoneurons; thus the joint firing probability of the motoneurons would be raised during the time course of the common EPSP. Furthermore, this effect would occur regardless of any synchronization between the pre-synaptic inputs themselves (pre-synaptic synchronization). The time course of short-term synchronization of motor unit discharges can be modelled on the assumption that it represents the joint increase in motoneuron firing probability that arises from the simultaneous arrival of common monosynaptic EPSPs (Kirkwood and Sears, 1978). In Kirkwood's model it was assumed that there was neither synchronization between the pre-synaptic elements nor time structure (e.g., periodicity) in their discharges. A variety of shapes of EPSP were used, the time course of the central correlogram peak ($f(t)$) could be accounted for by a weighted sum of the time course of the EPSP ($f(t)$) and its first temporal derivative ($df(t)/dt$). The actual weighting factors (a and b) being determined by the size of the EPSP and the level of synaptic noise which would be necessary to cause crossing of motoneuron firing threshold during its falling phase (see Gustaffson and McCrea, 1984; Kirkwood and Sears, 1991).

Datta and Stephens (1990) studied motor unit synchronization between pairs of first dorsal interosseous (1DI/1DI) motor units, recruited during isometric abduction of the index finger. They studied the time course of the central cross-correlogram peak through application of Kirkwood's model; from this they argued that its time course could be accounted for by

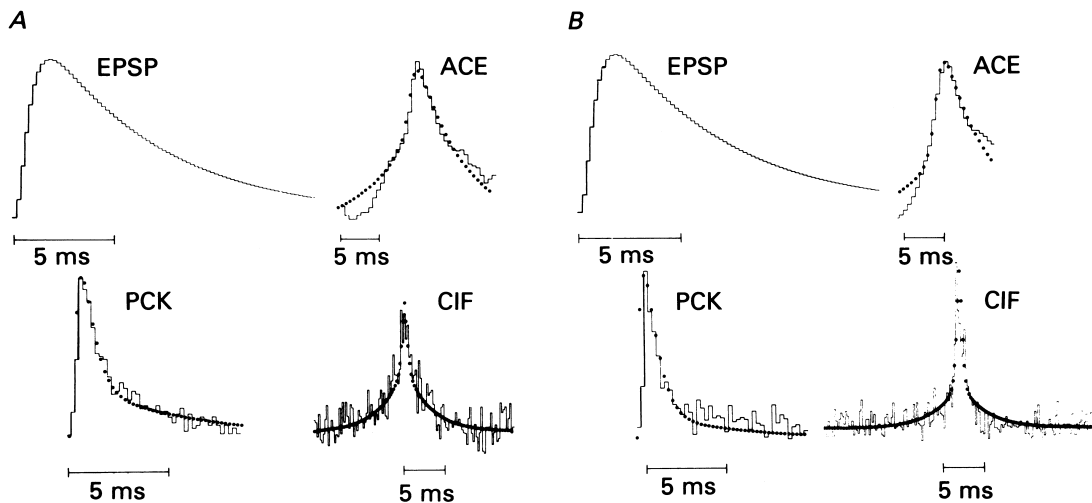


Fig. 1. Comparison of the time course of synchronization, as revealed by the cross-intensity function (CIF) between the discharges of pairs of single motor units observed in the human first dorsal interosseous muscle (1DI), with that predicted according to the theoretical model developed by P.A. Kirkwood (Kirkwood and Sears, 1978). *A* and *B*, (CIF continuous lines) represent data obtained from cross-correlating the discharges of two different pairs of single motor units recorded during isometric contraction of 1DI. The time course of the synchronization (CIF, continuous line) differs for the two motor unit pairs *A* and *B*. This is compared to the CIF time course derived theoretically (dotted line). EPSP time course given by the single compartment model of Rall et al. (1967) $f(t) = V\alpha^2(\beta - \alpha)^{-2}\{[(\beta - \alpha)t - 1]\exp(-\alpha t) + \exp(-\beta t)\}$ (for $t > 0$) (Edwards et al., 1976), with $\alpha = 15\beta$ in *A* and *B*, membrane time constant = 6 ms. Time course of raised probability of firing produced by EPSP in each motoneuron, primary correlation kernel (PCK, dotted line) given by $f'(t) = af(t) + bdf(t)/dt$, with $a = c$, $b = 0.35a$ in *A* and $a = c$, $b = 0.5a$ in *B*. Continuous lines for PCK in *A* and *B* replot experimental data from the cross-correlation histogram between the discharges of a primary-like muscle spindle afferent and the efferent discharges of α -motoneurons shown in Fig. 8E,C from Kirkwood and Sears (1982) for *A* and *B* respectively. Time course of average common excitation potential (dotted line, ACE) given by equations (v) and (vi), page 131 in Kirkwood and Sears (1978) using the same constants as for the respective PCKs in *A* and *B*. Continuous lines for ACE in *A* and *B* replot experimental data from the averaged naturally occurring intracellular synaptic noise of thoracic inspiratory motoneurons given in Fig. 12 of Kirkwood and Sears (1978). Time course of cross-intensity function (dotted line, CIF) given by equation (iv), page 130 in Kirkwood and Sears (1978) using the same constants as for the respective PCKs and ACES in *A* and *B*. Continuous lines for CIF in *A* and *B* plot pre- and post-stimulus time histograms recorded between the firing of two motor units in first dorsal interosseous muscle. Bin width: 0.39 ms, 4096 reference spikes.

common pre-synaptic drive from branched last order inputs delivering monosynaptic EPSPs. The types of fit between the model and human data are shown in Fig. 1, taken from Datta and Stephens (1990).

Other groups have detected short-term synchronization between low threshold motor units in a variety of muscles in man but have not necessarily used modelling to describe the cross-correlogram peak time course. Muscles in which short-term synchronization has now been detected include: sternocleidomastoid (Adams et al., 1989), masseter (Nordstrom et al., 1990) extensor digitorum communis (Bremner et al., 1991a; Schmied et al., 1993); elbow flexor muscles (Powers et al., 1989; Farmer et al., 1993b); extensor carpi ulnaris, radialis and deltoid (Deluca et al., 1993) and leg muscles (Datta et al., 1991; Davey et al., 1993; Neilsen and Kagami-hara, 1994; Gibbs et al., 1995). The majority of these studies detected short-term synchronization between motor units recruited at low (approximately 10% MVC) contraction strength. Recently, short-term synchronization has been described between motor units recruited at higher (30% MVC) contraction strengths (Deluca et al., 1993).

3. The muscle distribution of motor unit synchronization

As well as allowing inferences to be made concerning the time course of motoneuron EPSPs, cross-correlation analysis has been used to map the distribution of pre-synaptic inputs to human motoneurons. Kirkwood et al. (1982) demonstrated short-term synchronization between motoneuron activity recorded from different segments of the thoracic spinal cord in cat. This was interpreted as evidence for common pre-synaptic input to motoneurons of muscles that act as agonists, in this case those used in the act of breathing. Bremner et al. (1991a,b) conducted an extensive study of muscles acting on the human hand. They found evidence for short-term synchronization between a variety of muscles. Examples included the synchronization between motor units recorded in first and second dorsal interosseous muscles (1DI/2DI) or between motor units of first dorsal interosseous muscle and the index finger portion of flexor digitorum superficialis. The main point to arise from these studies was that distribution of common pre-synaptic input, as evidenced by the

presence of motor unit synchronization, conformed to a pattern that would, when activated, favour certain muscle synergies, for example, abducting the fingers or co-activating the thumb and index finger when engaging in a pincer grip. A second point to emerge was that the strength of the synchronization and, therefore, that of the common pre-synaptic input falls as recordings are made from more distant muscle pairs. For example, the strength of motor unit synchronization within any given subject falls by approximately 50% when comparing 1DI/1DI recordings to 1DI/2DI recordings. This was interpreted as evidence for focusing of last order pre-synaptic inputs to motoneurons. Recent studies have shown that, in contrast to homologous limb muscle pairs, which may be activated independently, homologous axial muscle pairs whose actions are closely related, for example left and right masseter, share common pre-synaptic inputs (Carr et al., 1994). Antagonist muscles in both upper and lower limbs do not show evidence of synchronization but rather may in some instances show reciprocal inhibition demonstrated as an area of decreased joint firing probability around time zero (Nielsen and Kagamihara, 1994; Gibbs et al., 1994). These studies illustrate the way in which inputs that provide voluntary pre-synaptic drive to motoneurons may be organised. The central nervous origin of the common synaptic inputs responsible for motor unit synchronization in man is next discussed.

4. The effects of central and peripheral lesions on motor unit synchronization

Patients with central nervous lesions have been studied in order to determine which types of motoneuron input may be involved in the generation of short-term motor unit synchronization. Recordings of motor unit activity from upper and lower limbs in patients with cortical, internal capsule or spinal cord lesions either due to cerebrovascular accident, neoplasia or trauma show both a loss and a change in the time course of motor unit synchronization, implying that central motor pathways are important in its generation (Datta et al., 1991; Farmer et al., 1993a; Davey et al., 1990). In comparison with the unaffected hand, the incidence of motor unit pairs showing significant synchronization in the affected hand of hemiparetic stroke patients was found to be reduced by approximately 40% (Farmer et al., 1993b). The amplitude of the cross-correlogram peaks detected was on average 50% smaller than that of the unaffected hand. The change in peak time course was particularly interesting. Typical changes in time course are illustrated in Fig. 2. Two effects were observed. First, in patients with mild strokes, usually of the internal capsule, the time course of the synchronization was found to be narrowed (see Fig. 2B). This

opened the possibility of modelling the time course in a similar fashion to that employed by Datta and Stephens (1990). An example of this approach is shown in Fig. 3. Here the time course of a peak detected in a healthy subject is modeled (Fig. 3A) and compared with the narrow time course obtained from a stroke patient (Fig. 3B). The interesting finding is that, in contrast to healthy subjects, some of these narrow peaks may be fit with a high (> 1) ratio of Kirkwood's PC operators b/a . Animal studies have shown that such peaks will arise when EPSPs are large compared with synaptic noise (Gustaffson and McCrea, 1984). Thus we have argued that following stroke, the EPSPs of some types of common pre-synaptic input respond by increasing in size with respect to the synaptic noise. A second effect was the broadening of the cross-correlogram peak time course such that it could no longer be modelled by

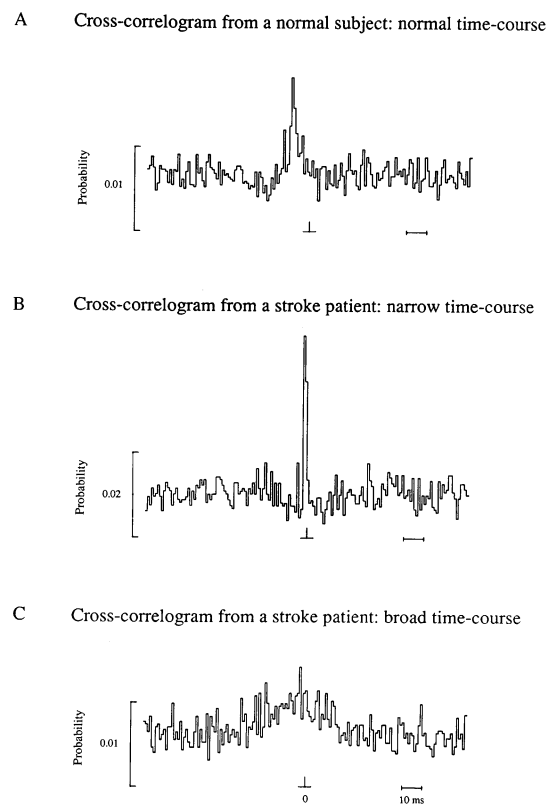


Fig. 2. Differences in the time course of central cross-correlogram peaks. *A*, cross-correlogram constructed between single motor unit discharges recorded from within 1DI in a healthy subject, displaying a normal time course consistent with the increase in joint motoneuron firing probability that results from the arrival of common EPSPs that are small with respect to synaptic noise. *B*, cross-correlogram between a pair of single motor unit discharges from the unaffected 1DI in a stroke patient, displaying an abnormally narrow central peak flanked by troughs of decreased firing probability. *C*, cross-correlogram between a pair of single motor unit discharges from the affected 1DI in a stroke patient displaying a broad-peak time course. Bin width in *A*, *B* and *C*, 1 ms. Reference spikes used for *A*, *B* and *C*, 4452, 1483 and 3298, respectively.

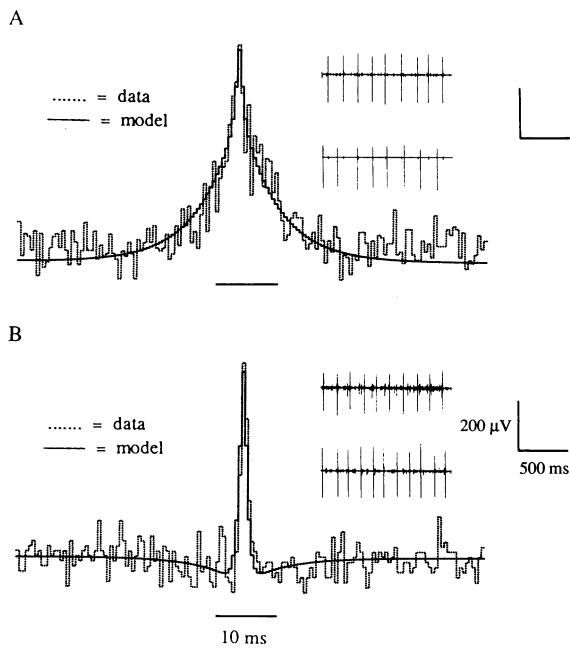


Fig. 3. The fit of Kirkwood's model to cross-correlograms constructed between single motor unit discharges recorded from within 1DI in *A*, a healthy subject and *B*, a stroke patient. The model time course is described by the continuous line and is fitted to the data displayed with a dotted line. Sample records of the motor unit data are displayed in the inserts. The EPSP parameter ratio (α/β) selected to model the data from the healthy subject was 20, corresponding to a common EPSP with 10–90% rise time 0.76 ms and half-width 5.52 ms; the PC operator ratio (b/a) used was 0.2. The EPSP parameter ratio (α/β) selected to model the data from the stroke patient was 15, corresponding to a common EPSP with 10–90% rise time 0.96 ms and half-width 5.89 ms; the PC operator ratio (b/a) used was 5.0. The number of reference spikes used in *A* and *B* were 2000 and 1483, respectively. Histogram bin width: 0.5 ms.

realistic EPSP parameters and PC operators (see Fig. 2C). This type of peak resembles that found following spinal cord transection in the cat (Kirkwood et al., 1984). The likely interpretation is that broad peak synchronization arises as a result of increased activity and synchronization between spinal interneurons which are either driven by non-corticospinal inputs or are released from descending inhibition, these then provide common (but not branched last order) pre-synaptic drive to the motoneurons. The output consequences of such broad peak synchronization would be expected to be a reduction in the independent control of motoneuron pools and an increase in tremor (Kirkwood and Sears, 1991; Logigian et al., 1988). Studies of stroke patients lead to the suggestions that in healthy subjects the inputs responsible for short-term synchronization arise centrally and that following CNS lesions plastic changes occur at the level of the motoneuron inputs that result in changes in the time course of the central cross-correlogram peak.

The hypothesis of centrally derived pre-synaptic input as the origin of motor unit synchroniza-

tion received further support from three further findings. First, it was found that motor units from first dorsal interosseus in a patient with severe peripheral deafferentation still displayed short-term synchronization (Baker et al., 1987; Farmer et al., 1993b). Second, in healthy subjects, it was shown that the number of motor units that display short-term synchronization and the strength of the synchronization detected declines when within muscle recordings are made from proximal muscles (e.g., biceps), compared with distal muscles (e.g., 1DI) (Farmer et al., 1993b). The results from the deafferented subject and this pattern of synchronization in healthy subjects would be expected only on the basis that the common drive arose from central (e.g., corticospinal) rather than spinal reflex (e.g., Ia afferent) pathways. Finally, the finding of short-term synchronization between only homologous left and right intrinsic hand muscles in a patient with congenital mirror movements, in whom there were bilateral rapidly conducting corticospinal inputs to hand muscle motoneurons, strongly suggested these inputs were an important pre-synaptic source involved in the production of short-term synchronization in healthy subjects (See Fig. 4 and Farmer et al., 1990b).

Recently, Kirkwood and Sears (1991) have argued that the central cross-correlogram peak duration detected in many human recordings is sufficiently broad to allow for the possibility of pre-synaptic synchronization involving at least one interneuron between the common pre-synaptic inputs and the motoneuron pair. They have suggested, on the basis of animal data, that cross-correlogram peak time courses of half-width 2.1 ms or less are the maximum in order to safely infer that the effect arises only from activity in last order common pre-synaptic inputs evoking common monosynaptic motoneuron EPSPs. It can be argued, however, that such extrapolations from cat experiments are problematic because the experimental and recording conditions are necessarily better controlled, the conduction delays along branches of last order common pre-synaptic axons may be less and, most importantly, levels of synaptic noise may be expected to be reduced compared to that expected in experiments on conscious human subjects.

We accept that these recent arguments concerning the exact interpretation of the time course of the peaks defined as short-term synchronization in man does indeed question whether hand muscle synergies are produced by activity in last order branched pre-synaptic inputs. However, the evidence discussed above strongly suggests that there exist in man a well focused group of common pre-synaptic inputs that are of corticospinal origin. We have proposed that distribution of short-term synchronization between different muscles in man may reflect the motoneuron distribution of divergent corticospinal axons and thus the muscle field of cortico-

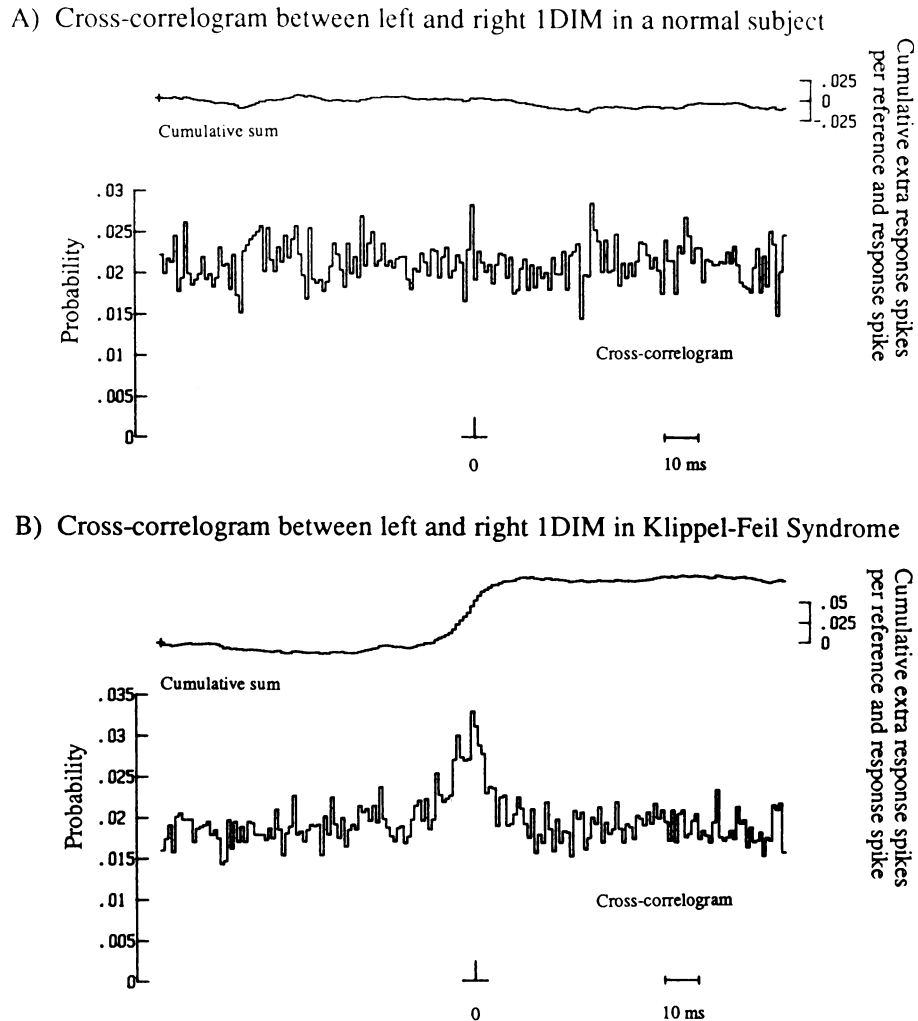


Fig. 4. *A*, cross-correlogram and cumulative sum constructed between single motor unit discharges simultaneously recruited from left and right 1DI muscles during steady voluntary co-abduction of the index fingers in a healthy subject. *B*, cross-correlogram and cumulative sum constructed between the discharges of a single motor unit recruited from left 1DI and those of a simultaneously recruited motor unit from right 1DI during steady voluntary co-abduction of the index fingers in a subject with Klippel-Feil syndrome and congenital mirror movements. In contrast to the correlogram obtained from the healthy subject, that obtained from the patient with mirror movements contains a central peak indicating that the left and right 1DI motoneurons share common presynaptic input. Number of reference spikes used in *A* and *B* were 3614 and 4769, respectively. Histogram bin width: 1 ms.

motoneurons, which encodes certain muscle synergies (Farmer et al., 1990b). There is ample evidence that focused but divergent direct corticospinal inputs to synergistic hand muscle motoneurons plays an important role in fine motor control in sub human primates (see Porter and Lemon, 1993 for review).

5. The effects of CNS lesions on the distribution of common motoneuron inputs

Cross-correlation analysis has been used to demonstrate activity in novel common pre-synaptic inputs in man that may arise either as the result of a develop-

mental anomaly of central motor pathways or following damage to one or other cerebral hemisphere. Farmer et al. (1990b) were able to demonstrate short-term synchronization between EMGs from homologous left and right muscle pairs in a patient with Klippel-Feil syndrome and congenital mirror movements (see Fig. 4). This effect was confined to the homologous muscle pairs and was not seen for non-homologous muscles. In this individual short-latency responses following transcranial electrical and magnetic brain stimulation were demonstrated at similar amplitude and latency in both left and right intrinsic hand muscles. Furthermore, in this subject was crossing of the long latency cutaneomuscular and stretch reflexes

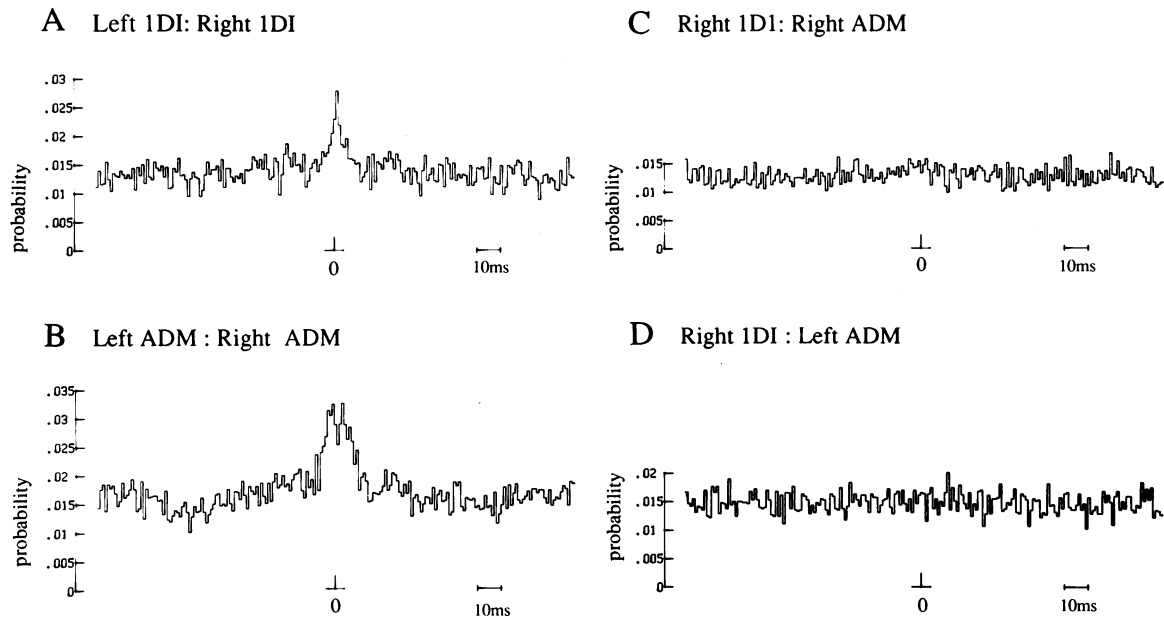


Fig. 5. Cross-correlograms constructed from multi-unit EMG activity recorded from the intrinsic hand muscles of a 14 year old patient with a congenital left hemiplegia and involuntary mirror movements. The patient spread the fingers of both hands such that simultaneous EMG was obtained from left and right 1DI and ADM muscles. *A* and *B*, the cross-correlograms between homologous left and right muscle pairs contain a peak at time zero, indicating the presence of common presynaptic input to the respective motoneuron pools. In contrast, no central peak is present in correlograms constructed between 1DI and ADM of the same hand, *C*, or between non-homologous left/right muscle pairs, *D*. Number of reference spikes used was 4500. Bin width: 1 ms.

(Farmer et al., 1990b; Matthews et al., 1990). These results were interpreted as evidence for abnormal common pre-synaptic inputs to left and right homologous motoneuron pools that were of corticospinal origin. It was suggested that activity in these pre-synaptic inputs produced the observed mirror movement. A similar study was performed on four children with congenital hemiplegic cerebral palsy and mirror movements (Farmer et al., 1991). In these children short latency EMG responses to magnetic brain stimulation could be evoked at similar latencies in both left and right intrinsic hand muscles following stimulation of the undamaged cerebral hemisphere only. Cross-correlation between on-going left and right hand muscle EMGs revealed evidence of synchronization of motor unit discharges and thus the presence of activity in common pre-synaptic inputs. These novel pre-synaptic inputs, it was felt, had either developed or persisted as a result of early unilateral damage to motor areas of the cerebral hemisphere. A more extensive study by Carr et al. (1993) confirmed and extended these findings and suggested that these novel inputs were present only if the cerebral damage occurred before the 27th week of gestation. The specificity of the abnormal common pre-synaptic inputs in these children was demonstrated by the fact that abnormal synchronization only occurred between muscle pairs that homologous, for example left and right 1DI. Simultaneous recordings of

multiunit EMG activity from left and right abductor digiti minimi (ADM) also showed synchronization between the homologous left and right muscle EMGs; however, no evidence of synchronization was detected between EMGs of either 1DI and ADM in the same hand or the corresponding left/right comparison (see Fig. 5, taken from Carr et al., 1993).

In summary, these experiments demonstrated the usefulness of cross-correlation analysis for the detection of activity in novel common pre-synaptic inputs to the two sides of the spinal cord and lead to the suggestion that activity in such inputs may aid the maintenance of corticospinal tract functions following unilateral brain damage.

6. Coherence between human motor units

Frequency domain analytical techniques when applied to point process data complement the more commonly used time domain measures and may emphasize different aspects of the data (Tukey, 1978; Brillinger et al., 1976; Rosenberg et al., 1989). Several groups have applied the frequency domain equivalent of cross-correlation analysis to human EMG recordings. Bruce and Ackerson (1986) demonstrated high frequency oscillations in the firing of respiratory muscle motoneurons. Elble and Randall (1976) demonstrated the motor unit

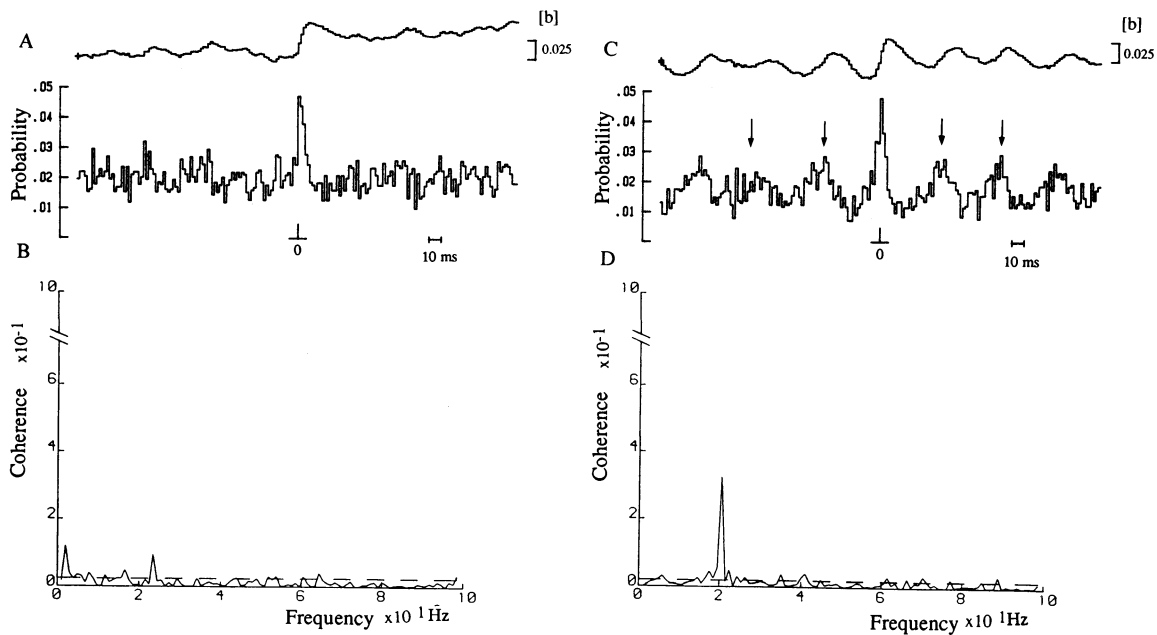


Fig. 6. Common modulation of the discharges of a pair of single motor units recorded from 2DI resulting from a periodic vibrational stimulus given to the belly of 1DI. *A*, Control cross-correlogram and cumulative sum constructed between the discharges of a pair of 2DI motor units. The cross-correlogram in *A* contains a central peak with no evidence of secondary peaks. *B*, the coherence spectra for the data used to construct the cross-correlogram in *A* show small peaks at 2 and 22 Hz. *C*, cross-correlogram and cumulative sum constructed between the discharges of the same pair of motor units used for *A* and *B*; in this case 20 Hz periodic vibrational stimuli were given to the belly of 1DI. The cross-correlogram contains a central peak and secondary peaks (shown by the arrows), these map symmetrically onto the cross-correlogram with an interpeak interval of approximately 50 ms. *D*, Coherence spectra for the data used to construct the cross-correlogram in *C*. A prominent peak at 20 Hz represents significant coherence between the motor unit discharges corresponding to the frequency of vibrational stimulation. The number of reference spikes used were 1180 for *A* and *B* and 1543 for *C* and *D*. Bin width *A* and *C*: 2 ms. Frequency resolution *B* and *D*: 1 Hz.

contribution to 8–12 Hz physiological tremor. We have concentrated on using coherence analysis of single motor unit activity recorded during isometric voluntary contraction of intrinsic hand muscles in order to detect periodic firing of common motoneuron inputs (Farmer et al., 1993a). An understanding of the mathematics of coherence analysis dictates that significant coherence between a pair of motor unit spike trains will imply some common periodicity of the pre-synaptic input. Empirical support for this interpretation in man was obtained by demonstrating that common modulation of motor unit firing due to periodic high frequency reflex afferent stimulation may be detected as coherence between the motor units at the frequency of stimulation (Farmer et al., 1990a). Fig. 6 (taken from Farmer et al., unpublished) shows the effects of periodic 20 Hz muscle vibration of first dorsal interosseous muscle on the coherence between two voluntarily recruited motor units recorded from second dorsal interosseous muscle (2DI). The two motor units in 2DI thus receive a common vibrator-dependent input via spinal reflex pathways, resulting in significant coherence between the motor units at 20 Hz and its harmonics. Interestingly, the size of the central peak in the cross-correlation histogram is little effected by the presence of muscle vibration (compare Fig. 6A and C). This would suggest

that the total drive to the motoneuron pair from common as opposed to non-common pre-synaptic inputs stays approximately the same. The subjects reported that during the vibration condition less subjective effort was required to maintain motor unit firing at the same rate. Thus we may speculate that during muscle vibration, reflex-driven common inputs provide a similar level of common drive to that of voluntarily-activated common inputs. This experiment points to an important difference in the way in which time and frequency domain approaches represent the same data, the coherence more clearly identifies the periodic component of the pre-synaptic input common to the motoneurons.

During voluntary isometric contraction in man coherence can be detected between pairs of 1DI motor units and between 1DI and 2 DI motor units in the frequency ranges 1–12 and 16–32 Hz (Farmer et al., 1993a; see Fig. 7). In addition, Davey et al. (1993) have described 17–24 Hz coherence between the discharges of tibialis anterior motor unit pairs. Particular interest has focused on the higher range of frequencies as these represent activity in common inputs that is in excess of the frequency of steady motor unit firing (usually in the range 8–12 Hz). The 16–32 Hz coherence represents common modulation of motoneuron firing frequencies that are not represented as discrete components in

the interval histogram of the motor unit spike trains and, therefore, can not be accounted for by the intrinsic periodic firing of the motoneurons or harmonics of this frequency. In this study the behavior of the pre-synaptic pathways that produce short-term motor unit synchronization and those responsible for 16–32 Hz coherence was found to be similar. Farmer et al. (1993b) were also able to demonstrate that the effect of the time course of common EPSPs on the coherence that may be detected between motor unit discharges is similar to that of a low pass filter, indicating that the time course of motoneuron EPSPs determines the upper limit of high frequency modulation of motor unit discharge. Thus it is further emphasized that time and frequency domain methods provide complementary ways of viewing motor unit data. Time domain techniques tend to integrate frequency domain information. The resulting cross-correlogram peak and secondary features are therefore highly sensitive to the time course of EPSPs and the spike generating properties of mo-

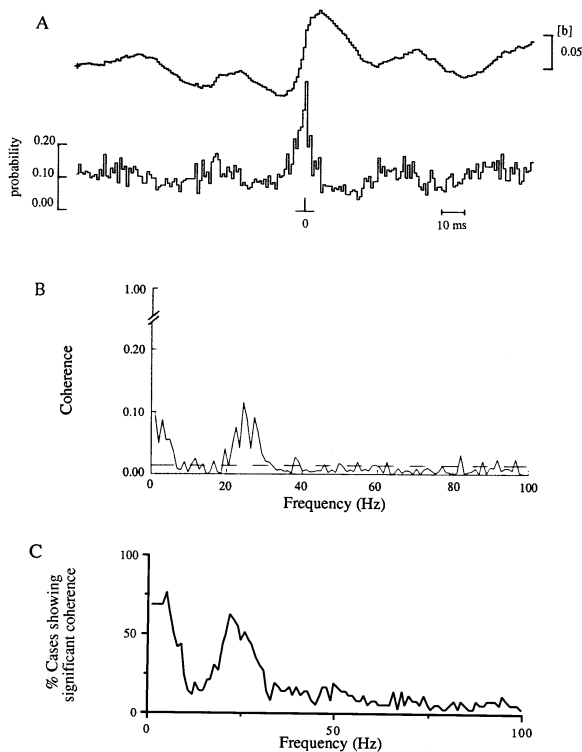


Fig. 7. *A*, cross-correlogram and cumulative sum constructed between the discharges of two single motor units recorded from within 1DI during a steady isometric contraction. *B*, coherence analysis performed on the same data. The central peak in *A* indicates motor unit synchronization; the coherence contains spectral components in the frequency ranges 1–7 and 18–29 Hz, indicating that the motor units are commonly modulated by inputs containing these frequency components. *C*, a histogram of the percentage of 37 motor unit pairs from 12 healthy subjects that contained a significant coherence peak at any given frequency in the range 1–100 Hz. Number of reference spikes used for *A* and *B* was 1945. Bin width for *A* was 1 ms. Frequency resolution *B* and *C* was 1 Hz.

toneurons but are less efficient at revealing common input periodicity. Frequency domain techniques are highly effective at revealing the different common input frequencies to motoneurons but are less explicit in revealing synaptic processes including EPSP characteristics and thus cannot distinguish readily between frequencies arising from activity in last order as opposed to interneuronal pre-synaptic inputs

Using arguments similar to those amassed for short-term synchronization Farmer et al. (1993b) suggested that coherence between motor units in the frequency range 16–32 Hz results from activity at these frequencies in central motor pathways including the corticospinal tract. Thus, like short term synchronization, 16–32 Hz coherence could be detected in a deafferented subject and was more prevalent and stronger between motor unit pairs recorded from distal as opposed to proximal upper limb muscles, a finding that argues against a role for Renshaw inhibition (see Davey et al., 1993). Furthermore, 16–32 Hz coherence was diminished in subjects who had suffered ischaemic damage to the corticospinal tract and primary motor cortex. Fig. 8 compares data obtained from a healthy subject to that obtained from a stroke patient. It can be seen in the case of the stroke patient both short-term synchronization and 16–32 Hz coherence are severely impaired. The graphs at the bottom of the figure compare the incidence of significant coherence peaks in the frequency range 1–100 Hz between healthy subjects (Fig. 8E) and patients who had suffered stroke contralateral to the hand from which motor unit recordings were made (Fig. 8F). The incidence of significant peaks is dramatically reduced in the stroke patient group. These findings were supported by the demonstration of a substantial reduction in the number of motor unit pairs with significant 16–32 Hz coherence in the affected hand of stroke patients, when compared to similar recordings from their unaffected hand.

Further evidence for the conjecture that the corticospinal tract is important in the production of 16–32 Hz coherence has come from the study of Mills and Schubert (1995). These authors found that, in contrast to short-term synchronization, 16–32 Hz coherence may be enhanced by the application of transcranial magnetic brain stimulation. Interestingly, these data also argue for a degree of functional dissociation between the processes that generate short-term motor unit synchronization and those involved in 16–32 Hz motor unit coherence. Direct evidence of cortical involvement in the production of 16–32 Hz motor unit coherence has been shown through simultaneous recording of EMG activity from 1DI muscle and magnetoencephalographic (MEG) activity from over the contralateral sensorimotor cortex during voluntary isometric index finger contraction in man (Conway et al., 1995b). This study demonstrated coherence between EMG and

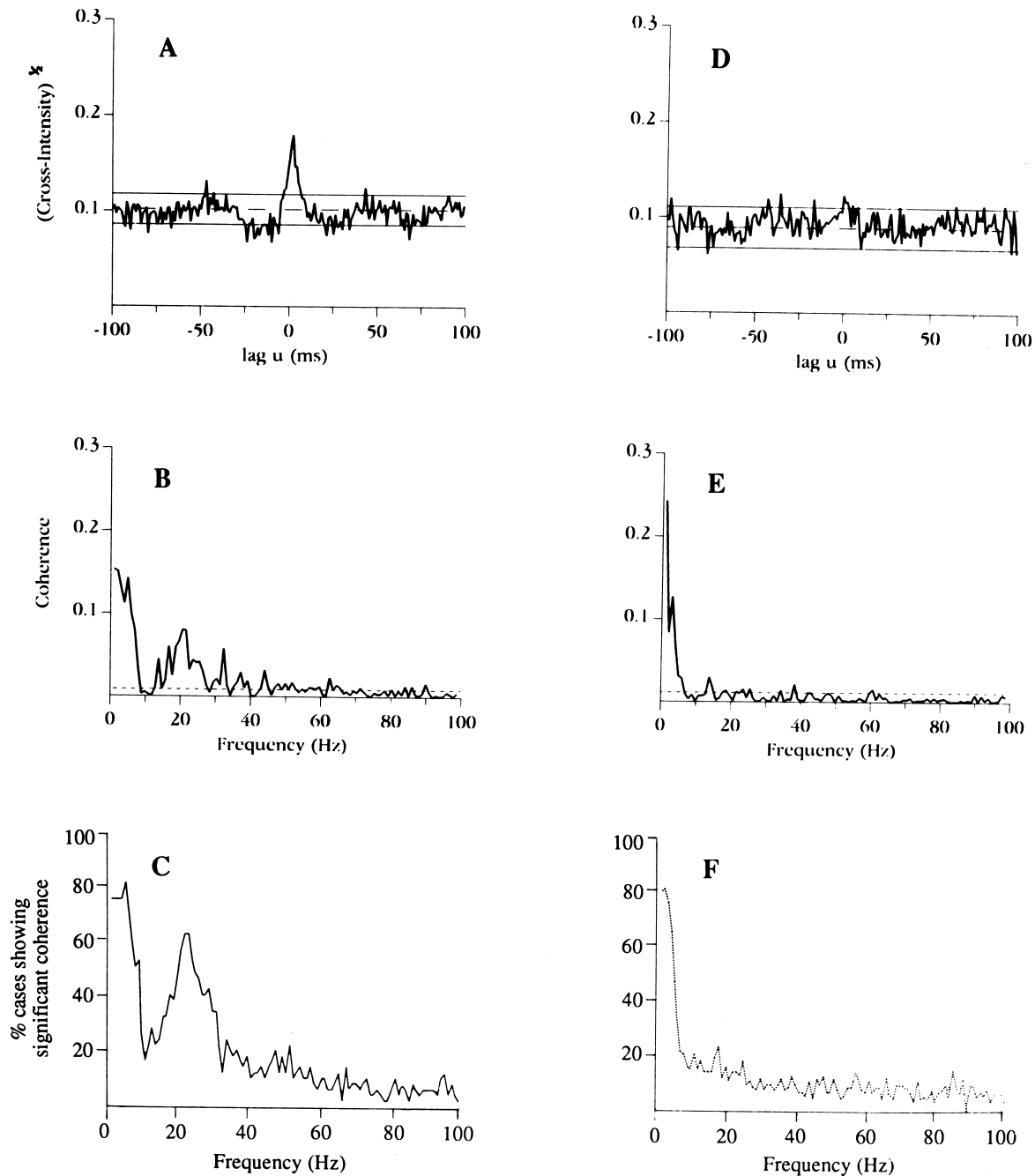


Fig. 8. *A*, cross-correlogram constructed between the discharges of two single motor units from within 1DI in a healthy subject. *B*, coherence for the data used to construct *A*. *D*, cross-correlogram constructed between the discharges of two single motor units recorded from within 1DI of the affected hand of a patient who had suffered an infarct in the contralateral internal capsule 4 months previously. *E*, coherence for the data used to construct *D*. The central peak in the cross-correlogram is absent in data recorded from the stroke patient. In contrast to the healthy subject, coherence is present only in the low frequency range in data obtained from the stroke patient. *C* and *F*, histograms of the percentage of motor unit pairs that show significant coherence at any given frequency in the range 1–100 Hz. *C*, data from 49 motor unit pairs in 16 healthy subjects; *F*, data from 91 motor unit pairs from the unaffected hand of 11 stroke patients. Number of reference spikes used was 1551 and 1168 for *A/B* and *D/E* respectively. Bin width for *A* and *D* was 1 ms. Frequency resolution for *B,C,E* and *F* was 1 Hz.

MEG in the frequency range 16–32 Hz, adding strong support for the hypothesis that coherence between two single motor unit spike trains in this frequency range results from periodic activity in common corticospinal

inputs. These findings lead us to propose that 16–32 Hz coherence between human motor unit discharges is a peripheral manifestation of rhythmic synchronization between neurons in the sensorimotor cortex and that

16–32 Hz frequencies may be involved in the temporal binding of distributed central and spinal motor systems.

7. Future directions and problems

The output consequences of motor unit synchronization and periodic firing of common motoneuron inputs have recently been re-evaluated using new measures of association. Particular attention has been paid to physiological finger tremor in man. It has been shown that in addition to the 8–12 Hz neurogenic component of physiological tremor there exists a component in the frequency range 16–32 Hz that is independent of inertial load and likely to reflect 16–32 Hz periodic firing of common motoneuron inputs (Conway et al., 1995a). In addition, using a new measure of association, the third order hybrid cumulant density function, it has been demonstrated that short-term synchronization of motor unit activity does indeed contribute directly to physiological tremor in man (Conway et al., 1994).

Several areas of the application of correlation analysis to human motor unit recordings are in need of further clarification. First, despite a recent valuable contribution to the literature (Nordstrom et al., 1992) there is still concern about the choice of the most appropriate index of synchronization strength and the behaviour of any such index with respect to regularity and rate of motor unit firing. Until agreement can be reached, quantitative studies of synchronization and cross-study comparisons are difficult. Second, the effects of motor task and ‘set’ need further work. There is some evidence that motor unit synchronization strength may be sensitive to task and may even be affected by volition (Adams et al., 1989; Bremner et al., 1991c; Schmied et al., 1993) but consistent effects have yet to be clearly identified. Finally, further work is needed on the interpretation of the time course of motor unit synchronization in man. Kirkwood and Sears (1991) have pointed out that the mere fact that the time course of certain peaks is well matched by equations that assume monosynaptic EPSPs does not exclude the fact that some part of the time-course of the peak may be accounted for by synchronization between discharges of pre-synaptic pathways that do not necessarily branch to produce last order input. The discovery that short-term synchronization co-exists with high frequency periodic activity in common pre-synaptic inputs now renders interpretation even more problematic. It should be noted that an explicit assumption in Kirkwood’s model was that there was no periodic structure in the firing pre-synaptic inputs (Kirkwood and Sears, 1978). High frequency periodic synchronization between non-branched pre-synaptic elements may well be expected to produce a common pre-synaptic input that is sufficiently tightly coupled to be able to generate the narrow

central peaks in cross-correlation histograms characteristic of short-term synchronization. Alternatively, it may be that it is branched last order pre-synaptic inputs that transmit high frequency rhythmic input to the motoneurons. We suggest that, in the future, interpretation of the time course of central cross-correlogram peaks may be aided by the combined application of time and frequency domain analytical methodology to motor unit spike train data. In the situation where common high frequency periodicities are detected between motor unit firing, interpretation of the time course of the central cross-correlogram peak may be problematic. Application of Kirkwood’s equations should be reserved perhaps for data in which frequency domain analysis has failed to reveal common high frequency periodicity. Further theoretical and modelling work is now required to aid interpretation of cross-correlogram peak time courses and their corresponding coherence spectra.

Despite some persisting difficulties of interpretation, the application of cross-correlational techniques to human motor unit recording over a breadth of problems in normal and abnormal motor control has yielding new, exciting and challenging insights into the organisation of the human motor system.

Acknowledgements

We thank Dr Lucinda Carr for allowing us to use her data for Fig. 5. Dr Farmer was supported by the Wellcome Trust.

References

- Adams, L. Datta, A.K. and Guz, A. (1989) Synchronization of motor unit firing during different respiratory and postural tasks in human sternocleidomastoid muscle, *J. Physiol.*, 413: 213–231.
- Adrian, E.D. (1947). General principles of nervous activity, *Brain*, 70: 1–17.
- Adrian, E.D. and Bronk, D.W. (1929). The discharge of impulses in motor nerves. Part II. The frequency of discharge in reflex and voluntary contractions, *J. Physiol.*, 67: 119–151.
- Baker, J.R., Bremner, F.D., Cole, J.D. and Stephens, J.A. (1987). Short-term synchronization of intrinsic hand muscle motor units in a deafferented man, *J. Physiol.*, 396: 155.
- Bremner, F.D., Baker, J.R. and Stephens, J.A. (1991a). Correlation between the discharges of motor units recorded from the same and from different finger muscles in man, *J. Physiol.*, 432: 355–380.
- Bremner, F.D., Baker, J.R. and Stephens, J.A. (1991b). Variation in the degree of synchronization exhibited by motor units lying in different finger muscles in man, *J. Physiol.*, 432: 381–399.
- Bremner, F.D., Baker, J.R. and Stephens, J.A. (1991c). Effect of task on the degree of synchronization of intrinsic hand muscle motor units in man, *J. Neurophysiol.*, 66: 2072–2083.
- Bigland, B. and Lippold, O.C.J. (1954). Motor unit activity in the contraction of human muscle, *J. Physiol.*, 67: 119–151.

- Brillinger, D.R., Bryant, H.L. and Segundo, J.P. (1976). Identification of synaptic interactions, *Biol. Cybernet.*, 22: 213–228.
- Bruce, E.N. and Ackerson, L.M. (1986). High-frequency oscillations in human electromyograms during voluntary contractions, *J. Neurophysiol.*, 56: 542–553.
- Buchtal, F. and Honke, P. (1944). Electromyographic examination of patients suffering from poliomyelitis ant. ac. up to 6 months after the acute stage of the disease, *Acta Med. Scand.*, 116: 148–164.
- Buchtal, F. and Madsen, A. (1950). Synchronous activity in normal and atrophic muscle, *Electroencephalogr. Clin. Neurophysiol.*, 2: 425–444.
- Carr, L.J., Harrison, L.M., Evans, A.L. and Stephens, J.A. (1993). Patterns of central motor reorganization in hemiplegic cerebral palsy, *Brain*, 116: 1223–1247.
- Carr, L.J., Harrison, L.M. and Stephens, J.A. (1994). Evidence for bilateral innervation of certain homologous motoneuron pools in man, *J. Physiol.*, 475: 217–227.
- Conway, B.A., Farmer, S.F., Halliday, D.M. and Rosenberg, J.R. (1994). Higher-order analysis of the contribution from correlated motor unit discharges to physiological tremor, *J. Physiol.*, 479: 30.
- Conway, B.A., Farmer, S.F., Halliday, D.M. and Rosenberg, J.R. (1995a). On the relation between motor unit discharge and physiological tremor. In A. Taylor, M.H. Gladden, and R. Durbaba, (Eds.), *Alpha and Gamma Motor Systems*, Plenum, New York, pp 596–598.
- Conway, B.A., Halliday, D.M., Farmer S.F., Shahani, U., Maas, P. Weir, A.I. and Rosenberg, J.R. (1995b). Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man, *J. Physiol.*, 489: 917–924.
- Datta, A.K. and Stephens, J.A. (1990). Short-term synchronization of motor unit activity during voluntary contraction in man, *J. Physiol.*, 422: 397–419.
- Datta, A.K., Farmer, S.F. and Stephens, J.A. (1991). Central nervous pathways underlying synchronization of human motor unit firing studied during voluntary contractions, *J. Physiol.*, 432: 401–425.
- Davey, N.J., Ellaway, P.H., Friedland, C.L. and Short, D.J. (1990). Motor unit discharge characteristics and short-term synchrony in paraplegic humans, *J. Neurol. Neurosurgery Psychiatry*, 53: 764–769.
- Davey, N.J., Ellaway, P.H., Baker, J.R. and Friedland, C.L. (1993). Rhythmicity associated with a high degree of short-term synchrony of motor unit discharge in man, *Exp. Physiol.*, 78: 649–661.
- Deluca, C.J., Roy, A.M. and Erim, Z. (1993). Synchronization of motor unit firings in several human muscles, *J. Neurophysiol.*, 70: 2010–2023.
- Dengler, R., Wolf, W., Birk, P. and Struppler, A. (1984). Synchronous discharge in pairs of steadily firing motor units tend to form clusters, *Neurosci. Lett.*, 47: 167–172.
- Dietz, V., Bischofberger, E., Wita, C. and Freund, H.-J. (1976). Correlation between the discharges of two simultaneously recorded motor units and physiological tremor, *Electroencephalogr. Clin. Neurophysiol.*, 40: 97–105.
- Edwards, F.R., Hirst, G.D.S. and Silinsky, E.M. (1976). Interactions between inhibitory and excitatory synaptic potentials at a peripheral neuron, *J. Physiol.*, 259: 647–663.
- Elble, R.J. and Randall, J.E. (1976). Motor-Unit activity responsible for 8 to 12 Hz component of physiological finger tremor, *J. Neurophysiol.*, 39, 2: 370–383.
- Farmer, C., Farmer, S.F., Halliday, D.M., Rosenberg J.R. and Stephens, J.A. (1990a). Coherence analysis of motor unit firing recorded during voluntary contraction in man. *J. Physiol.* 420: 22.
- Farmer, S.F., Ingram, D.A. and Stephens, J.A. (1990b). Mirror movements studied in a patient with Klippel-Feil syndrome, *J. Physiol.*, 428: 467–484.
- Farmer, S.F., Harrison, L.M., Ingram, D.A. and Stephens, J.A. (1991). Plasticity of central motor pathways in children with hemiplegic cerebral palsy, *Neurology*, 41: 1505–1510.
- Farmer, S.F., Swash, M., Ingram, D.A. and Stephens, J.A. (1993a). Changes in motor unit synchronization following central nervous lesions in man, *J. Physiol.*, 463: 83–105.
- Farmer, S.F., Halliday, D.M., Rosenberg, J.R. and Stephens, J.A. (1993b). The frequency content of common synaptic inputs to motoneurons studied during voluntary isometric contraction in man, *J. Physiol.*, 470: 127–155.
- Fulton, J.F. and Liddell, E.G.T. (1925). Electrical responses of extensor muscles during postural (myotatic) contraction, *Proc. R. Soc. B*, 98: 577–589.
- Gibbs, J., Harrison, L.M., Mayston, M.J. and Stephens, J.A. (1994). Short-term antisynchronization of motor unit activity in antagonist muscles in man, *J. Physiol.*, 476: 20.
- Gibbs, J., Harrison, L.M., and Stephens, J.A. (1995). Organization of inputs to motoneuron pools in man, *J. Physiol.*, 485: 245–256.
- Gordon, G. and Holbourn, A.H.S. (1948). The sound of single motor units from human forearm muscles during voluntary isometric contractions, *J. Physiol.*, 107: 456–464.
- Gustaffson, B. and McCrea, D. (1984). Influence of stretch-evoked synaptic potentials on firing probability of cat spinal motoneurons, *J. Physiol.*, 347: 431–451.
- Hoefler, P.F.A. and Putman, T.J. (1940). Action potentials of muscles in rigidity and tremor, *Arch. Neurol. Psychiatry*, 43: 704–725.
- Kirkwood, P.A. and Sears, T.A. (1978). Synaptic connections to intercostal motoneurons as revealed by the common excitation potential, *J. Physiol.*, 275: 102–134.
- Kirkwood, P.A. and Sears, T.A. (1982). The effects of single afferent impulses on the probability of firing of external intercostal motoneurons in the cat, *J. Physiol.*, 322: 315–336.
- Kirkwood, P.A., Sears, T.A., Stagg, D. and Westgaard, R.H. (1982). The spatial distribution of synchronization of intercostal motoneurons in the cat, *J. Physiol.*, 327: 137–155.
- Kirkwood, P.A., Sears, T.A. and Westgaard, R.H. (1984). Restoration of function in external intercostal motoneurons of the cat following partial central deafferentation, *J. Physiol.*, 350: 225–251.
- Kirkwood, P.A. and Sears, T.A. (1991). Cross-correlation analyses of motoneuron inputs in a coordinated motor act. In Kruger, J., (Ed.) *Springer Verlag Series in Synergetics: Neuronal Cooperativity*, Springer Verlag, Berlin, Heidelberg, pp. 225–248.
- Kranz, H. and Baumgartner, G. (1974). Human alpha motoneuron discharge, a statistical analysis, *Brain Res.*, 67: 324–329.
- Logigian, E.L., Wierzbicka, M.M., Bruyninckx, F., Wiegner, A.W., Shahahi, B.T. and Young, R.R. (1988). Motor unit synchronization in physiologic, enhanced physiologic, and voluntary tremor in man, *Ann. Neurol.*, 23: 242–250.
- Matthews, P.B.C., Farmer, S.F. and Ingram, D.A. (1990). On the localization of the stretch reflex in a patient with mirror movements, *J. Physiol.*, 428: 561–577.
- Mills, K.R. and Schubert, M. (1995). Short term synchronization of human motor units and their responses to transcranial magnetic stimulation, *J. Physiol.*, 483: 511–523.
- Milner-Brown, H.S., Stein, R.B. and Lee, R.G. (1975). Synchronization of human motor units: possible roles of exercise and supraspinal reflexes, *Electroencephalogr. Clin. Neurophysiol.*, 38: 245–254.
- Moore, G.P., Segundo, J.P., Perkel, D.L. and Levitan, H. (1970). Statistical signs of synaptic interaction in neurons, *Biophys. J.*, 10: 876–900.
- Neilsen, J. and Kagamihara, Y. (1994). Synchronization of human leg motor units during co-contraction in man, *Exp. Brain Res.*, 102: 84–94.
- Nordstrom, M.A., Fuglevand, A.J. and Enoka, R.M., (1992). Estimating the strength of common input to human motoneurons from the cross-correlogram, *J. Physiol.*, 453: 547–574.
- Nordstrom, M.A., Miles, T.S. and Turker, K.S. (1990). Synchronization of motor units in human masseter a prolonged isometric contraction, *J. Physiol.*, 426: 409–421.

- Person, R.S. and Kudina, L.P. (1968). Cross correlation of electromyograms showing interference patterns, *Electroencephalogr. Clin. Neurophysiol.*, 25: 58–69.
- Person, R.S. and Mishin, L.S. (1964). Auto and cross correlation analysis of the electrical activity of muscles, *Med. Electr. Biol. Eng.*, 2: 155–159.
- Piper, H. (1912). *Electrophysiologie menschlicher*, Springer, Berlin.
- Porter, R. and Lemon, R. (1993). Corticospinal function and voluntary movement. *Monographs of the Physiological Society* 45. Oxford University Press, New York.
- Powers, R.K., Vanden Noven, S. and Rymer, W.Z. (1989). Evidence of shared direct input to motoneurons supplying synergist muscles in humans, *Neurosci. Lett.*, 102: 76–81.
- Rall, W., Burke, R.E., Smith, T.G., Nelson, P.G. and Frank, K. (1967). Dendritic location of synapses and possible mechanisms for the monosynaptic Epsp in motoneurons, *J. Neurophysiol.*, 30: 1169–1193.
- Rosenberg, J.R., Amjad, A.M. Breeze, P., Brillinger, D.R. and Halliday, D.M. (1989). The Fourier approach to the identification of functional coupling between neuronal spike trains, *Prog. Biophys. Mol. Biol.*, 53: 1–31.
- Rothwell, J.C. (1994). *Control of human voluntary movement*. Chapman Hall, London.
- Schmied, A., Ivarsson, C. and Fetz, E.E. (1993). Short-term synchronization of motor units in extensor digitorum communis muscle: relation to contractile properties and voluntary control, *Exp. Brain Res.*, 97: 159–172.
- Sears, T.A. and Stagg, D. (1976). Short-term synchronization of intercostal motoneuron activity, *J. Physiol.*, 263: 357–381.
- Taylor, A. (1962). The significance of grouping of motor unit activity, *J. Physiol.*, 162: 259–269.
- Tukey, J.W. (1978). Can we predict where time series should go next? In Brillinger, D.R. and Tiao (Eds.), *Institute of Mathematical Statistics—Reports on Directions Time Series*, Iowa State University, Ames, pp. 1–31.