EFFECT OF TRAINING ON CORTICOSPINAL CONTROL OF HUMAN MOTOR UNITS

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CONTENTS

ABSTRACT

The influence of different muscle usage patterns on corticospinal control of human motor units (MUs) was studied during voluntary isometric abduction of the index finger to activate the first dorsal interosseous (FDI) muscle. The primary aim was to quantify any control differences in MUs from hands which had been trained over many years, and to determine if any observed differences in these hands influenced the precision of force production.

Measures of correlated MU discharge patterns were different in FDI muscles of individuals with different hand preferences, and in individuals trained over many years for skill- or strength-related tasks. The mean strength of MU synchronization was weak, and of equivalent strength in both hands of skill-trained subjects and the dominant (skilled) hand of untrained right-handed (RH) subjects. A second measure of correlated MU discharge (common drive), which was found to arise from a separate mechanism to that of MU synchronization, was also weaker in skill-trained subjects compared to untrained and strength-trained subjects. A reduction in both measures of correlated MU discharge in skill-trained subjects indicate that certain features of the neural control of the FDI motoneuron pool are different in these individuals.

As corticospinal inputs are likely to be important for MU synchronization, transcranial magnetic stimulation (TMS) was used as a more direct measure of hemispheric differences in corticospinal excitability. TMS over each hemisphere in untrained RH subjects revealed that the corticospinal inputs controlling FDI were more active, and therefore contributed relatively more to the net excitatory command, when the non-dominant hand was used to perform index finger abduction. These hemispheric differences in corticospinal excitability were sufficient to explain the differences in MU synchrony in dominant and non-dominant hands during comparable low-force contractions. It is likely that reduced synchrony in 'skilled' hands is due to a reduced excitability of corticospinal inputs to the FDI motoneuron pool when these hands are used to perform the simple index finger abduction task.

The amplitude of the tremor force fluctuations of the index finger were much lower in skill-trained subjects. However, the weaker MU synchrony observed in these subjects was not responsible for the reduced force tremor, as correlations between the overall extent of MU synchrony and tremor were weak, and all non-significant.

Results from this thesis support the view that neural control of FDI muscle is different in individuals with different patterns of long-term muscle use. This enhances the possibility that a specific, short-term training regimen can modify the neural control of muscles, and is an area which warrants future investigation.

DECLARATION

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

To the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference is made in the text.

I consent to this thesis being made available for photocopying and loan.

John G. Semmler

November, 1996

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AIMS AND GENERAL INTRODUCTION

While there is quite a lot of information on how training may influence muscle strength and endurance, this has focussed almost exclusively on the physiological and biochemical changes occurring in muscle fibres. There is relatively little information on the effects of training on the neural control of movement. The intention of this thesis is to provide evidence of a training-related effect on neural control of a muscle in individuals who have long-standing different patterns of use of their muscles. If evidence can be obtained indicating that neural control differences exist in these groups, it would suggest that it is worthwhile to examine the effects of specific training programs on the neural control of force.

The activation of motor units (MUs), which are the smallest functional elements of neuromuscular control, provides the final output pathway of the motor system. Large differences in the activation patterns of MUs are evident in different individuals, and it is the discharge properties of the MUs which have the potential to influence the precision of force production. It is possible that an extended period of muscle use for certain tasks may alter MU discharge properties, which may reflect altered neural control strategies in these individuals. The major aim of this thesis was to examine the MU discharge properties (discharge rate, variability, synchronization, common drive) in first dorsal interosseous muscle of individuals who, through many years of selective use or practice, had experienced very different usage patterns of their hand muscles. The control of muscles of the hand that move the fingers is very impressive, in that they are capable of being activated in a fractionated manner necessary for performing remarkably skilled tasks requiring independent control of the digits. The neural substrate for this ability is the large number of direct corticospinal projections onto motoneurons of intrinsic hand muscles. In Chapter 2, the influence of hand preference on MU discharge properties of an intrinsic hand muscle (the first dorsal interosseous muscle) has been examined in right- and left-handed subjects, while in Chapter 4, these MU discharge properties have been assessed in individuals who regularly perform skill- (musicians) or strength-trained (weightlifters) activities. As corticospinal

inputs are important for fine control, and for MU synchronization, it was initially hypothesised that MU synchronization would be greater in the dominant (skilled) hand of untrained right-handed subjects, and both hands of skill-trained subjects. As reported in Chapters 2 and 4, this hypothesis was not correct, and MU synchrony was found to be weaker in the skilled hands.

A second aim of this thesis was to explore the relationship between different muscle usage patterns and involuntary force fluctuations (tremor). I examined whether the neural control differences among individuals contributed to systematic differences in tremor force fluctuations. It was anticipated that force fluctuations would be larger as a result of certain MU discharge characteristics (e.g. MU synchrony), but the extent to which different discharge properties influence the precision of force production is currently unknown. Systematic differences in tremor force fluctuations related to muscle use, and the influence of MU discharge properties on tremor in the same individuals have been examined in Chapters 2 and 4.

Two forms of correlated MU discharge, MU synchronization and common drive, reveal features of shared synaptic inputs to motoneurons during a voluntary isometric contraction. Although it is likely that widely divergent, branched axons from single corticomotoneuronal cells are the most important inputs responsible for MU synchronization, the source of the common drive is not known. A further aim of this thesis was to evaluate the importance of the shared branched-axon inputs to motoneurons in the production of common drive. This was performed by comparing MU synchronization and common drive in the same MU pairs during the same trial of voluntary MU discharge. The results of this analysis are presented in Chapter 3.

The relationship between two different measures of MU synchronization were also investigated. Although the technique of cross-correlation of MU discharges is generally regarded as the most reliable estimate of MU synchrony, training-related alterations in MU synchronization have only been examined previously in one study which used a less direct measure of synchronous MU activity obtained from the surface electromyogram (EMG). At

present, it is not clear whether the estimates of MU synchronization revealed by the two methods are equivalent, and represent a manifestation of the same physiological processes. A comparison of the estimate of MU synchronization using the cross-correlation and surface EMG methods is shown for the same MU pairs in Chapter 5.

The final aim of this thesis was to determine whether hemispheric differences exist in motor cortex excitability during muscle activation in hands consistently used for different tasks. This study was prompted by the results obtained in experiments described in Chapter 2, which revealed reduced MU synchronization in the dominant (skilled) hand in untrained right-handed subjects. This finding may represent a reduced strength or divergence of direct corticospinal inputs to the dominant hand of untrained right-handed subjects, or a reduced excitability of the corticospinal neurons when the dominant hand was used to perform the task. Transcranial magnetic stimulation provides information on the excitability of corticospinal neurons, and this technique was used to assess the latter hypothesis. From experiments performed on resting muscle, several lines of evidence suggest that there are hemispheric differences in corticospinal excitability, but this does not provide information on the activity of corticospinal neurons during a voluntary motor task. Corticospinal neurons play a major role in the fine control of individual digits, and it is possible that the operation of this pathway during voluntary activity is related to fine motor control in dominant and non-dominant hands. In Chapter 6, transcranial magnetic and electrical stimulation (which activate the corticospinal pathway at different sites) have been used to examine hemispheric differences in corticospinal effectiveness during muscle activation for simple index finger abduction. It was hypothesised that the corticospinal neurons in the hemisphere controlling the dominant hand were relatively less active during this task than their counterparts in the other hemisphere when the non-dominant hand was used. If confirmed, hemispheric differences in motor cortex excitability in this task may explain the reduced MU synchrony in the dominant hand of untrained right-handed subjects (Chapter 2).

CHAPTER 1

LITERATURE REVIEW

1.1 Single motor units

The single motor unit (MU) is the final output pathway of the motor system, and is the means by which we interact with the external environment. A single MU is the smallest functional component of muscle, consisting of a motoneuron, its axon and the muscle fibres innervated by that axon. The muscle fibres of a single MU are controlled by one axon, and therefore must contract and relax as one functional unit. The number of muscle fibres per MU can vary from about 20 in finely controlled muscles such as the extraocular muscles (Burke, 1981), to as many as 1600 in large postural muscles such as the medial gastrocnemius (Feinstein *et al.* 1955). In adult humans, all muscle fibres of a single MU lie within a single anatomically defined muscle (Stuart & Enoka, 1984), however the muscle fibres of the MU are scattered over part of the cross-section of the muscle. The territory occupied by the entire unit is between 20 - 30% of the mean cross-sectional area of the muscle, or 15% of the total muscle volume (Burke, 1981). Therefore, muscle fibres of one MU are neither distributed over the entire muscle nor are they concentrated into one localised area.

Intramuscular recording of MU activity has become a common occurrence since its introduction in the late 1920's (Adrian & Bronk, 1929; Denny-Brown, 1929). Recording single MU activity is performed by inserting an electrode into the muscle and recording the action potentials of the muscle fibres associated with one MU. The impetus for recording from single MUs is that the firing properties of the motoneuron can be inferred from the discharge of the MU. This is possible for two reasons. Firstly, all fibres of the MU are

activated by each motoneuron discharge, because of the high safety factor for transmission at the neuromuscular junction (Bigland-Ritchie *et al.* 1979). Secondly, in mammalian muscle, a given muscle fibre is innervated by a single motoneuron (Burke, 1981). This relationship between the motoneuron and the muscle fibre provides the investigator with a relatively simple means of gaining information about the discharge characteristics of motoneurons whose cell bodies lie within the spinal cord. In the present series of investigations, recordings of single MU discharge were undertaken in individuals with different, and sometimes specialised long-term muscle usage patterns. Differences in MU activation patterns in these individuals were used to infer adaptations in the neural control of muscles as a result of continual long-term training procedures.

1. 1. 1 Motor unit types

Most muscles contain muscle fibres with differing contractile speeds. As all muscle fibres comprising a single MU have virtually identical biochemical characteristics, muscle fibres with different contractile speeds belong to different MUs. Most muscles are composed of MUs with a range of properties. These different properties can be categorised with either histochemical, biochemical or physiological techniques, and either method results in equivalent MU sub-groups (Burke, 1981). Physiologically, MUs can be classified on the basis of their time to peak twitch tension, peak tetanic tension, the conduction velocity of the motor axons and their fatigability. These physiological MU properties can be used as a relatively simple and reliable assessment of the MU properties of the muscle (Stein *et al.* 1972; Milner-Brown *et al.* 1973b; Taylor & Stephens, 1976; Garnett *et al.* 1979).

Different MUs have a broad range of physiological properties, with the simplest classification divided into two main types. Type S fibres generally correspond to slow-twitch, fatigue resistant fibres, while type F fibres have varying degrees of fatiguability. Generally, type S fibres are recruited earlier, produce a small force output, have long contraction times and slow conducting motor axons. In contrast, type F fibres are recruited later, produce the largest force, have short contraction times and fast conducting motor axons. Based on these criteria, the fibre type composition of a muscle is usually an indicator

of its function, with postural muscles containing a high degree of slow-twitch, fatigue resistant fibres (type S) and muscles consistently required for ballistic contractions exhibit a high degree of fast-twitch, fatigable fibres (type F).

1. 1. 2 Control properties of motor units

The critical factor in the control of force during a voluntary contraction is the strategy for activating the smallest functional component of muscle; the MUs. The central nervous system (CNS) has two mechanisms to generate and modulate muscle force during a voluntary contraction. The first mechanism relies on the orderly recruitment of MUs for the control of force. The second mechanism is primarily involved with the modulation of firing rates of the already active MUs. Both recruitment and firing rate modulation are utilised in parallel to varying extents during a voluntary contraction.

1.1.2.1 The orderly recruitment of motor units

The strategy of MU recruitment used for force production has received much attention. Although notable earlier studies on the MU recruitment scheme exist (Liddell & Sherrington, 1925; Denny-Brown & Pennybacker, 1938), the greatest contribution to the recruitment literature has been provided by Henneman and colleagues since the late 1950's. The main emphasis of their experimental work was to determine the sequence of activation of motoneurons in the decerebrate cat in the reflex response evoked by muscle stretch. These experiments have established that there is a highly reproducible order of motoneuron recruitment and de-recruitment which is not influenced by the rate of stretch or by the type of input (Henneman *et al.* 1965a; Henneman *et al.* 1965b). These studies have indicated that the pattern of recruitment is size dependent, with the motoneurons with the smallest soma and slower conducting axons being recruited first and the largest motoneurons with fast-conducting axons recruited last. Although exceptions to this rule exist (Kanda *et al.* 1977; Garnett & Stephens, 1981), it is now well accepted that during reflexly-evoked contractions in animals (Henneman *et al.* 1965a; Henneman *et al.* 1965b) and reflex and voluntary contractions in humans (Milner-Brown *et al.* 1973b; Calancie & Bawa, 1985), this 'size

principle' of motoneuron recruitment is extremely consistent and reproducible.

One important aspect related to the size principle of motoneuron recruitment is the parameter which determines the orderly recruitment. According to Henneman and colleagues, the major component of the recruitment order is based simply on cell size. As small motoneurons have a higher input resistance (Katz & Thesleff, 1957), they require less excitatory drive in the form of synaptic currents to be activated. A similar input to all motoneurons of a motoneuron pool would preferentially activate the smallest motoneurons first, as the voltage threshold for an action potential is similar for all motoneurons (see Henneman & Mendell, 1981). However, many studies have indicated that a number of factors combine to determine a motoneuron's recruitment threshold. These include the organisation of the synaptic input to the motoneurons (where evidence exists that the smallest Ia motoneurons receive greater synaptic input than larger Ia motoneurons (Burke & Rymer, 1976)), and the interaction of this input with the size and other biophysical properties of the cell (such as the absolute voltage threshold for action potential generation, absolute resting membrane potential, membrane accommodation to depolarising currents and membrane processes controlling refractoriness (see Henneman & Mendell, 1981 for a review)). It is now generally accepted that multiple factors must be considered in an explanation of the orderly recruitment of motoneurons.

Irrespective of the critical determinant of the motoneuron recruitment threshold, we can be reasonably confident that motoneurons are recruited in order of size under normal conditions of activation in voluntary isometric contractions. Such an arrangement frees the nervous system from individual control of single motoneurons; a concept which was thought possible in early work (Forbes, 1922) but is now known to be impracticable due to the large number of conceivable motoneuron recruitment combinations, even within one muscle (see Henneman & Mendell, 1981). The solution to the process of orderly recruitment is based on the overall pattern of synaptic connections and inputs to the motoneurons. For instance, it has been demonstrated that both the corticospinal (Shinoda *et al.* 1979) and muscle spindle (Mendell & Henneman, 1968) afferents branch widely to innervate most if not all of the

motoneurons in the target muscle. Therefore, when excitation to the motoneuron pool increases, there is a wide divergence of excitatory synaptic current to the motoneurons innervating a given muscle.

Along with the removal of the need to control motoneurons individually, the process of orderly recruitment provides many functional advantages (see Stuart & Enoka, 1984). Small motoneurons, which are recruited first, innervate slow twitch (type S) muscle fibres which produce the lowest force and fatigue only slowly during prolonged contractions. Large motoneurons, which are recruited last, innervate fast twitch (type F) muscle fibres which produce the greatest force but fatigue rapidly. During weak prolonged contractions such as those required for postural stabilisation, it is appropriate that the small motoneurons are recruited first. During short periods when a contraction becomes more forceful, the larger motoneurons are recruited to perform the task. Therefore, the sequence of activation of motoneurons is well matched to the force requirements of the task, and the appropriate activation strategy transpires to minimise the influence of fatigue. Also, the increment in force with each newly recruited MU increases with the total force, which is important for the precision of force control.

1.1.2.2 Motor unit discharge rate modulation

In contrast to MU recruitment, the concept of firing rate modulation of MUs to modify force levels has received considerably less attention. This has been due to the technical difficulty of obtaining reliable recordings to allow accurate discrimination of MU action potentials. Recently, techniques have been developed to extract the individual MU action potentials from the complex intramuscular MU recording during contractions at both low (Türker *et al.* 1989) and high force levels (LeFever *et al.* 1982; LeFever & De Luca, 1982). These techniques have allowed information to be obtained about the range of discharge rates in different human muscles during various tasks.

Although differences exist in the MU discharge characteristics between animals and humans (see Burke, 1981 for details), it is generally agreed that MUs begin to discharge tonically at

between 6-12 Hz (Monster & Chan, 1977). Maximal discharge rates, however, are much more variable, depending on the species under investigation, the muscle being tested, and the experimental conditions. In human limb muscles, the maximum tonic firing rate is usually around 15-30 Hz (Woods *et al.* 1987). The firing rates of motoneurons activating very fast muscles, such as the extraocular muscles, have been shown to have instantaneous discharge rates up to 1000 Hz (Henn & Cohen, 1972). On the whole, the maximum firing rates can vary from 15 Hz to around 50 Hz during steady voluntary contractions in humans, depending on the muscle (Bigland & Lippold, 1954; Person & Kudina, 1972; Milner-Brown *et al.* 1973c; Freund *et al.* 1975; Monster, 1979). The different ranges of steady firing rates exhibited in different human muscles was clearly shown by Tokizane & Shimazu (1964). These authors have indicated that small distal muscles tend to exhibit higher maximum frequencies than proximal muscles, and a similar pattern is seen with rostral compared to caudal muscles.

The relationship between the MU discharge rate and the force produced by a muscle has been addressed by a number of investigators. These reports have indicated that the firing rates of active MUs increase proportionally with increasing force (Person & Kudina, 1972; Milner-Brown *et al.* 1973c; Monster & Chan, 1977). It is the wide divergence of the inputs to the motoneuron pool which promotes a uniform increase in firing rate of active MUs, and frees the nervous system from individual control of MU discharge rates. This is the same concept that neatly explains the recruitment of MUs according to the size principle (see 1.1.2.1)

1.1.2.3 Recruitment *vs.* rate modulation

Both recruitment and firing rate modulation are important factors in the control of muscle force. The relative contributions of each depend on the structure and function of the muscle under investigation. Small muscles (such as intrinsic hand muscles) are generally involved in performing fine movements which require small incremental changes in force. In such muscles, all MUs are typically recruited in the initial 50% of a maximal voluntary contraction (MVC) and further force increases are established by increases in the discharge rates of the active MUs (Milner-Brown *et al.* 1973c; Kukulka & Clamann, 1981; De Luca *et al.* 1982a).

In contrast, large muscles (such as biceps brachii and deltoid) are generally involved in either producing large forces or in controlling posture. In these muscles, recruitment of additional MUs has been shown to occur at levels up to 88% MVC (Kukulka & Clamann, 1981), indicating that MU recruitment is the major force producing component. Based on these findings, it has been suggested that rate-coding offers advantages when accurate movements are required, as smaller increments can be added to the total force output. Recruiting additional MUs has a tendency to produce a 'staircase effect' in the force output (De Luca, 1985), which would not be advantageous for finely controlled tasks. To optimise the pattern of MU control, it appears that the nervous system has developed a strategy to balance the degree of recruitment- or rate-coding depending on the number of MUs, the muscle fibre composition, and the task that the muscle is generally required to perform.

1.2 The first dorsal interosseous muscle

Intrinsic muscles of the hand play an important role in fine, independent control of the digits. The neural mechanisms which contribute to this ability are discussed in detail in section 1.3. Of the intrinsic hand muscles, the first dorsal interosseous (FDI) muscle has been studied extensively for a number of years, and has been the primary muscle of interest in many neurophysiological studies of human motor control. This is because the FDI possesses a number of advantages over other intrinsic hand muscles. For example:

i) The FDI is a small muscle which lies superficially on the dorsal aspect of the hand between the index finger and thumb. This makes it easily accessible for electromyographic (EMG) examination.

ii) The anatomical arrangement of the FDI makes it the only muscle capable of abducting the index finger (Eyler & Markee, 1954; Landsmeer & Long, 1965).

iii) Its nerve supply, the deep branches of the ulnar nerve, can be readily stimulated with surface electrodes.

iv) Morphological estimates from cadavers indicate that the FDI consists of

approximately 120 MUs with approximately 340 muscle fibres in each MU (Feinstein *et al.* 1955). The FDI has a balanced composition of muscle fibres with 57% classified as type S and 43% classified as type F (Johnson *et al.* 1973). This indicates that the muscle has an intermediate function, and could be used for both prolonged contractions (without readily fatiguing) and strong ballistic contractions.

v) The FDI also acts as a synergist to other muscles during flexion of the metacarpophalangeal joint (Eyler & Markee, 1954; Landsmeer & Long, 1965). Therefore, the FDI is active during tasks such as the precision grip (object held between thumb and index finger), and is also active during tasks which require strong contractions, such as the power grip. These tasks, or slight variations of them, are used during normal daily activities. For example, hand writing can be considered as training for a precision grip task, where the fine control of a pen held between thumb and index finger is a critical determinant of the outcome. As the FDI is involved in all movements of the index finger except for extension (Brand *et al.* 1981), undertaking normal daily activities which include precision and power grips result in training effects in this muscle.

It is for these reasons that the FDI is an ideal muscle to study the control of human MUs, and has been used as the muscle of interest in the present series of investigations.

1. 2. 1 Anatomy of the first dorsal interosseous muscle

The FDI is an anatomically confined small muscle with estimated volumes of 7 - 9 cm^3 (Keen *et al.* 1994). The FDI is a bipennate muscle which has a central tendon and has muscle fibres arising from the ulnar aspect of metacarpal I and the radial aspect of metacarpal II and inserts, on the radial side, into the capsule of the metacarpophalangeal joint and the base of the proximal phalanx of the index finger (Landsmeer & Long, 1965). The muscle fibres from metacarpal I vary in length from 2.5 to 3.5 cm (average 3.1 cm) while the fibres from metacarpal II have a uniform length of approximately 1.6 cm (Brand *et al.* 1981). The angle of pennation of these muscle fibres has been estimated at 9.2° (Jacobson *et al.* 1992).

1. 2. 2 Control properties of motor units in the first dorsal interosseous muscle

The first comprehensive study on the activation sequence of MUs in human FDI was conducted by Milner-Brown *et al.* (1973b) who endeavoured to correlate the contractile properties of FDI MUs estimated using spike triggered averaging (STA) with recruitment force during voluntary isometric contractions. These authors showed that twitch contraction times for FDI MUs varied from 30 to 100 ms, with over 80% having twitch contraction times less than 70 ms. The twitch tensions of FDI MUs estimated by STA vary widely from 0.01 - 0.26 N (Milner-Brown *et al.* 1973b; Stephens & Usherwood, 1977). In the later study, Stephens & Usherwood (1977) combined MU contractile properties with the fatigue resistance characteristics of the MUs. These authors reported that MUs recruited at contraction strengths < 0.5 N had relatively low twitch tensions (0.02 - 0.19 N), long contraction times (59 - 146 ms) and were non-fatigable. MUs recruited at higher contraction strengths (> 2 N) had higher twitch tensions (0.15 - 0.26 N), faster contraction times (33 - 57 ms) and were highly fatigable. It was concluded from this work that MUs of the FDI are recruited in order of increasing contraction strength (at least in the tested range 0 - 20 N) combined with a reduction in fatigue resistance.

Freund *et al.* (1975) have shown that MUs in FDI commence tonic firing once recruited at an average (± SD) rate of 6.8 ± 1.4 Hz. As a result of this study, consensus seems to exist that MUs within FDI discharge at around 6-8 Hz when activated just above their recruitment threshold, which is in the lower range of tonic discharge rates of MUs in human muscles (Monster & Chan, 1977). The low discharge rate for MUs within FDI is consistent with the minimal tonic discharge rates of other intrinsic hand muscles, such as adductor pollicis (6 Hz, Kukulka & Clamann, 1981) and flexor pollicis brevis (6 Hz, Ivanova *et al.* 1986), and muscles of the upper (extensor digitorum communis, 8 Hz, Monster & Chan, 1977; biceps brachii, 5 Hz, Denier van der Gon *et al.* 1985) and lower limbs (rectus femoris, 5 Hz, Person & Kudina, 1972; tibialis anterior, 7 Hz, Andreassen & Rosenfalck, 1980). The maximal discharge rate of FDI MUs has been reported to be approximately 50 Hz (De Luca *et al.* 1982a; Kamen *et al.* 1995) indicating that the FDI has a much larger range of tonic

discharge rate than large postural muscles such as the soleus (6 -10 Hz, Mori, 1973).

The relative contribution of recruitment- and rate-coding is known to be specific to the muscle investigated. In FDI, recruitment is the main mechanism to produce force at low contraction levels, with the bulk of recruitment occurring in the first half of an MVC (Milner-Brown *et al.* 1973c). At higher force levels, increased firing rate becomes the more important mechanism for force modulation and constitutes the major mechanism for force modulation if the entire physiological range is considered (Milner-Brown *et al.* 1973a; Milner-Brown *et al.* 1973c).

1.3 The corticospinal component of the pyramidal tract

Distal muscles of the upper limb such as the FDI are unique because they are able to perform movements involving precise and selective use of individual digits. One factor which has a high correlation with this ability is the relatively large number of direct corticospinal projections to motoneurons controlling muscles involved in fine control (Porter & Lemon, 1993). Given this relationship, it is likely that skill differences between hands would be reflected in structural and/or functional differences in corticospinal projections to skilled and unskilled hands. It is an aim of the present series of experiments to determine whether the long-term use of a hand for skilled or unskilled tasks results in differences in measures of corticospinal function, such as the corticospinal responses evoked following magnetic stimulation of the motor cortex (see section 1.3.3.4), and the strength of synchronous MU discharge within a muscle (see section 1.4).

1. 3. 1 The origin, course and projections of the corticospinal tract

The corticospinal tract consists of fibres originating from the cerebral cortex which continue to the spinal cord. Therefore, it is a direct pathway from the cortex to the spinal cord. Corticospinal fibres originate in both motor and sensory regions of cerebral cortex. The majority of corticospinal fibres have their origins from a restricted region of the cerebral

cortex, and are provided by the axonal processes of pyramidal cells within lamina V (Catsman-Berrevoets & Kuypers, 1976; Jones & Wise, 1977). In mammals, the primary motor cortex contributes more fibres to the corticospinal tract than any other region (Porter & Lemon, 1993). In animals, the technique of retrograde labelling neurons after injections of horseradish peroxidase or fluorescent tracers has enabled an accurate assessment of the origins of corticospinal fibres. Using such methods, Toyoshima & Sakai (1982) have shown in the monkey that approximately 63% of corticospinal fibres arise from the precentral gyrus (51% motor cortex [area 4], 12% premotor cortex [area 6]) and the remaining 37% from the parietal lobe, especially the somatic sensory cortex. In man, Jane *et al.* (1967) counted the number of fibres in the pyramidal tract of a 51 year old patient in whom the precentral gyrus had been removed surgically 20 years earlier. The ipsilateral pyramid had a fibre count that was 40% of the intact, contralateral pyramid, suggesting that about 60% of the tract must be derived from the precentral gyrus (areas 4 and 6). In man, it is generally agreed that there is an even split of corticospinal projections from the motor cortex (30%) and premotor cortex (30%), with the remaining 40% of fibres arising from the parietal lobe.

In all mammals, corticospinal fibres arise from these pre- and post-central regions of cerebral cortex and descend through the internal capsule. They then join the cerebral peduncle, which is the fibre bundle that forms the inferior portion of the midbrain. The fibres of the corticospinal tract which terminate at various levels of the spinal cord descend into the medullary pyramids. However, the level of pyramidal decussation, the relative proportion of fibres that cross and the length of these fibres, vary from one species to the next (Verhaart, 1948). In humans, the lateral corticospinal tract decussates just after it passes below the dorsal column nuclei in the medulla. In the decussation, about 90% of the corticospinal axons cross the midline to reach the contralateral corticospinal column, where they descend to the appropriate level and location within the spinal cord.

On the basis of differential projections to various regions of the spinal cord, Kuypers (1981) divided the mammalian species into 4 main groups. In most of the marsupials (group 1), the

corticospinal fibres extend only to cervical and mid-thoracic segments and terminate in the dorsal horn. In carnivores such as the cat and dog, and some New World monkeys (group 2), the corticospinal fibres extend throughout the spinal cord and terminate in the dorsal horn and the intermediate zone. In most of the New and Old World monkeys (group 3), the corticospinal fibres extend throughout the spinal cord and terminate in the dorsal horn, intermediate zone and parts of the lateral motoneuronal cell groups. In man and the great apes (group 4), the lateral corticospinal fibres project to sensory neurons in the dorsal horn (laminae IV and V), to interneurons in the intermediate zone and to motoneuron pools (alpha and gamma) innervating upper and lower limb muscles (Nathan & Smith, 1955; Kuypers, 1960; Kuypers, 1981; Nathan *et al.* 1990). The ventral shift of the connections in higher primates provides access to the ventral horn of the spinal cord via corticospinal connections, but is accompanied by less dense projections to the dorsal horn.

The corticospinal fibres that project to the dorsal horn originate in different areas of the cerebral cortex than do those that project to the intermediate zone and to motoneurons. The neurons that project to the dorsal horn (via the lateral corticospinal tract) are located in the somatic sensory cortex of the post-central gyrus. Those projecting contralaterally to the lateral parts of the intermediate zone and to the motoneurons that innervate distal limb muscles are located in the motor areas of the precentral gyrus (areas 4 and 6), principally in regions controlling arm and leg muscles. The ventral corticospinal tract consists of corticospinal fibres which do not decussate at the medullary level. The ventral corticospinal tract projects to motoneuron pools innervating axial and proximal muscles as well as to the adjoining portions of the intermediate zone. Unlike the lateral tract, the ventral corticospinal fibres commonly have a bilateral projection to motoneurons on both sides of the spinal cord which cross at spinal cord level.

1. 3. 2 The fibres of the corticospinal tract

Although the distribution of corticospinal fibre diameters is monotonic, it is generally considered that two types of fibres (known as fast and slow corticospinal fibres) exist within the corticospinal tract. The fastest corticospinal fibres are large diameter (11-20 μm),

myelinated fibres which have conduction velocities of approximately 50 - 60 ms^{-1} (and up to 80 ms^{-1}; Levy *et al.* 1984) and constitute only a small proportion (~2%) of the corticospinal tract. Slow corticospinal fibres make up over 90% of the corticospinal tract. The slowest corticospinal fibres are unmyelinated and have axon diameters of 1-4 μm with conduction velocities of approximately 14 ms^{-1} (Kuypers, 1981; Rothwell, 1987).

All primates possess a large pyramidal tract containing many corticospinal fibres. In man, the numbers of fibres has been estimated at approximately 1.1 million (see Heffner & Masterton, 1975). It has been demonstrated that there is a precise relationship between body weight and the number of corticospinal fibres (Towe, 1973), although fibre number has been shown to correlate poorly with dexterity (Heffner & Masterton, 1975). The exact proportion of corticospinal neurons which make direct contact with motoneurons is unknown, but based on estimates using physiological methods (see Porter & Lemon, 1993), the number is believed to be small. Difficulties with sampling techniques prevent an accurate estimate. Although approximately half of the fast corticospinal fibres (Fetz & Cheney, 1980), and a smaller percentage of slow corticospinal fibres may make direct contact with spinal motoneurons, this number is relatively small compared to the number of cortical output neurons in layer V of cerebral cortex.

1. 3. 3 Corticomotoneuronal cells and fine control of finger movements

In the corticospinal system, there are large differences in the number and sizes of fibres, and their course, pattern and distribution in the spinal cord. The relationship of these features of corticospinal tract organisation to motor capacity has been subjected to detailed tests in primates. These studies have indicated conclusively that a monosynaptic projection to spinal motoneurons exists, and that the corticospinal projections are preferentially involved in finely graded movements, rather than gross movements of the limbs. These investigations have been diverse in their techniques, and will now be discussed in more detail below.

1.3.3.1 Electrophysiological studies

Intracellular recordings in individual spinal motoneurons has provided the opportunity to

make observations of the activation and organisation of afferent pathways to motoneurons. Bernhard *et al.* (1953) were the first to suggest that direct inputs from the cortex to motoneurons were concerned with skilled hand function. Through electrical stimulation of the cortex in the monkey, they were able to measure the time of arrival of the corticospinal volley in the spinal cord. When recording the response time from the spinal cord to the muscle, and the total time taken from the cortex to the muscle, they were able to indicate that a monosynaptic connection between the cortex and spinal motoneurons existed. The authors devised the term 'corticomotoneuronal' (CM) fibres, to describe the nature of the direct cortical inputs that they had demonstrated.

Preston & Whitlock (1961) were the first to obtain a record of CM excitation based on intracellular recordings of post-synaptic potentials from individual motoneurons. They discovered after weak electrical stimulation of the cortex, that excitatory post-synaptic potentials (EPSPs) and inhibitory post-synaptic potentials (IPSPs) were detected in spinal motoneurons of the monkey. Although in some cases the responses were complex, containing both EPSPs and IPSPs, most motoneurons displayed excitatory responses which had a latency consistent with a monosynaptic connection from the motor cortex. Similarly, by stimulating the arm and hand area of the baboon motor cortex, Landgren *et al.* (1962a; 1962b) established consistent excitatory monosynaptic events on the target motoneurons. It was established through this work, that all CM connections from the motor cortex were excitatory. Evidence has been obtained that short-latency inhibition is established via disynaptic pathways involving spinal interneurons (Jankowska *et al.* 1976), with a delay of the inhibitory response, due to the extra synapse, ranging from 1.2 to 1.5 ms (Landgren *et al.* 1962a; Landgren *et al.* 1962b).

Since intracellular studies have demonstrated the nature of the monosynaptic connection to motoneurons, it is also of interest to examine the distribution of these corticospinal connections onto the active motoneurons. The nature (amplitude and latency) of the post-synaptic potential indicates the number of direct projections (and/or boutons) from the corticospinal neurons. This may provide some evidence as to the importance the motor

cortex places on the direct activation of various motoneuron pools, and may help in determining the function of the corticospinal projections. Earlier studies have indicated that the distribution of monosynaptic excitation from the fast pyramidal tract fibres favour more distal hand and forearm motoneurons than the more proximal muscles of the upper arm (Phillips & Porter, 1964; Clough *et al.* 1968; Fritz *et al.* 1985). The largest responses to motor cortex stimulation (up to 5 mV) were recorded in motoneurons of intrinsic hand and the finger extensor muscles, while smaller responses (1 mV) were recorded in upper arm muscles.

1.3.3.2 Behavioural Studies

Correlations between structure and function of the corticospinal pathway have been sought by making lesions of the corticospinal pathway in the adult animal at a specified stage of its development. These studies have attempted to carry out tests to determine the deficits in motor performance which could be detected after the lesions were made. When the upper limb is affected by stroke or lesion, human studies have revealed that hand movements are usually more seriously affected than are movements involving more proximal parts (Colebatch & Gandevia, 1989). In animal studies, it was Lawrence & Kuypers (1968a; 1968b) who provided the best evidence available for the functional significance of the corticospinal terminations among motoneurons innervating distal muscles. They examined the effects of bilateral section of the pyramidal tract (at the medullary level) on the motor skills of macaque monkeys. They followed the behaviour of the monkeys for several months after a complete lesion of the pyramidal tract not involving other nearby structures. It was established that, without the influence of corticospinal projections (and other pyramidal projections from non-corticospinal fibres) the general motor behaviour of the animals was normal, but they had completely lost the capacity to produce independent finger movements. It was apparent that the monkeys had permanently lost the ability to produce independent control of the distally acting muscles to perform precision grip, but these distal muscles could still be used, apparently normally, in grasping for objects (using a power grip i.e. using all fingers in a sweeping motion), climbing and collecting food. After unilateral

lesion of the pyramidal tract, essentially the same outcome occurs in the contralateral limb.

1.3.3.3 Anatomical Studies

A number of behavioural studies on animals have indicated that some species have the ability to perform independent movements of the digits while others do not. In the cat or rat, independent use of the digits is absent. In the New World monkey, there is pseudo-opposition of the thumb and index finger. In the Old World monkey, the hand is used for grasping objects and manipulating them, such that true opposition is present. However, object manipulation and dexterity are best developed in chimpanzee and man.

One aspect of corticospinal innervation which has a high correlation with dexterity is the number of direct corticospinal terminations to the ventral horn of the spinal cord. The descending cortical pathways to the spinal cord differ in different species with respect to both their trajectories and their terminal distribution. Species with the highest index of dexterity (including the ability to perform a thumb-index opposition) have numerous corticospinal terminations in the ventral horn. Species in which functional corticospinal connections are sparse or absent are less dexterous. Anatomically, corticospinal connections to the ventral horn are denser and more extensive in chimpanzees than in monkeys (Kuypers, 1964) and are even more prominent in man (Schoen, 1969). Anatomical evidence for corticospinal terminations in the vicinity of motoneurons clearly indicates that these are more dense in the vicinity of motoneurons innervating muscles acting distally (Porter, 1987). These observations provide further support that corticospinal projections from the primary motor cortex to the ventral horn of the spinal cord, are, at least in part, necessary for the fine control of independent finger movements.

1.3.3.4 Neurophysiological studies

1.3.3.4.a Spike triggered averaging and cross-correlation

The STA technique has been used to identify the presence of a monosynaptic connection from the cortex to spinal motoneurons and the functional significance of these connections to

the control of movement. In relation to control of intrinsic hand muscles, this method consists of assessing the increased probability of firing of motoneurons controlling a hand or wrist muscle in a monkey with respect to the firing of a pyramidal tract neuron (PTN) during a voluntary task. If a monosynaptic CM connection exists between the PTN and the motoneuron, the EPSPs produced in a population of motoneurons by impulses in the PTN should raise their firing probability and show a peak in the surface EMG average at the appropriate latency. This peak is commonly known as post-spike facilitation (PSF). There is a substantial body of evidence to suggests that PSF effects are mediated by direct CM projections. This evidence primarily concerns the latency of PSF.

The latency of PSF is consistent with the estimated conduction time over the fast corticospinal pathway (Fetz & Cheney, 1980; Lemon *et al.* 1986; Lemon, 1993). Initial experiments used STA from the PTN to the surface EMG of the muscle of interest (Fetz *et al.* 1976). However, the onset latency of PSF in the averaged surface EMG could not be determined with the precision required to suggest a monosynaptic pathway was involved. Using cross-correlation analysis of the tonically active PTN and a single MU from an intrinsic hand muscle, the onset latency of PSF from the cross-correlation histogram peak can be measured more precisely than in the STA. Following voluntary activation of single MUs, the onset latency between corticospinal fibres and single MUs has been found to be similar to the latency produced in the same MU by weak stimulation of the medullary pyramids (Lemon, 1993). In contrast, longer PSF latencies have been established from PTNs which have been shown not to make monosynaptic connections with motoneurons. These include motor cortex non-PTNs (Lemon *et al.* 1986), PTNs which terminate in the dorsal horn of the spinal cord (Widener & Cheney, 1988) and motor cortex PTNs in non-primates such as rats and cats which generally lack direct CM connections (Armstrong & Drew, 1984). Further evidence comes from the observation that PTNs with rapidly conducting axons generate PSF with shorter latencies than those with slow axons (i.e. < 30 ms^{-1}; see Porter & Lemon, 1993), and the absence of PSF from neurons lacking direct corticospinal connections (Widener & Cheney, 1988). From this evidence, it seems reasonable to suggest that the earliest peaks in the PSF for pyramidal tract stimulation are

derived from the activation of CM cells.

The STA technique has also been used to determine the role of the direct corticospinal projection, by recording the discharge of the cortical cells of origin of the pyramidal tract and correlating it with the amplitude of the PSF during various tasks (Evarts, 1965; Hardin, Jr., 1965; Evarts, 1966). These studies in the cat and monkey have indicated that corticospinal cells show greater changes in firing rate during finely adjusted and controlled movements than they do for large, ballistic movements. Furthermore, Cheney & Fetz (1980) have shown that corticospinal cells are more active at the start of a movement, and during modulations in force, than during tonic holds. More recently, it has been clearly demonstrated that corticospinal neurons are more active during a precision grip than during a power grip (Muir & Lemon, 1983; Lemon *et al.* 1986). This occurs despite the fact that the EMG is usually much greater during the power grip. These findings, combined with the idea that monosynaptic facilitation is greater to motoneurons of distal hand muscles than those of forearm muscles (Lemon *et al.* 1986), indicates that the direct corticospinal projection is preferentially involved in control of fine movements. The role of the direct corticospinal projection in gross movements of the limbs is much less, indicating that the motoneurons must receive most of their synaptic excitation from other, indirect sources during the task.

1.3.3.4.b Cortical Stimulation

Studies on the exposed motor cortex in primates indicate that electrical stimulation of the brain produces short latency muscle evoked potentials (MEPs) of the contralateral muscles of the hand and forearm. In intact, awake human subjects, transcranial electrical stimulation (TES) over the motor cortex also produces short latency MEPs in contralateral limb muscles (Merton & Morton, 1980; Marsden *et al.* 1983; Rothwell *et al.* 1987) at latencies consistent with the activation of rapidly conducting corticospinal pathways (Rothwell *et al.* 1987). As the largest corticospinal fibres have the fastest conduction velocities, the earliest responses to TES would arise from the activation of fast corticospinal fibres. Estimates of the rise times of the EPSPs were short, indicating that the corticospinal neurons activated by TES make

monosynaptic connections with spinal motoneurons (Zidar *et al.* 1987; Day *et al.* 1989).

The human motor cortex can also be stimulated without the discomfort produced by electrical stimulation, by using a rapidly changing magnetic field to generate electrical currents in the brain (Rothwell *et al.* 1991). Transcranial magnetic stimulation (TMS) over the motor cortex produces short latency contractions of contralateral muscles, similar to those produced by TES (Hess *et al.* 1987; Mills *et al.* 1987). The responses to TMS have latencies that are 1-2 ms longer than the responses to TES (Hess *et al.* 1987). Some experimenters have argued that the latency difference occurs because TES activates corticospinal neurons directly, whereas TMS activates the corticospinal pathway trans-synaptically (Hess *et al.* 1987; Day *et al.* 1989). Given that the background level of excitation of the corticospinal neurons influences the size of the descending corticospinal volley, the different sites of activation of TMS (trans-synaptic) and TES (direct corticospinal activation) indicates that the amplitude of the MEP following TMS is more sensitive to changes in excitability of the motor cortex than the MEP following TES (Day *et al.* 1989).

TMS has been used to indicate whether the short latency activation of MUs in contralateral hand muscles occurs via a monosynaptic connection. For intrinsic hand muscles, the majority of MUs display a short latency facilitation (see Rothwell *et al.* 1991 for a review). Through estimation of the central conduction velocities (50 - 80 ms^{-1}; Levy *et al.* 1984) and the rise times of the underlying compound EPSPs (3 - 5.5 ms; see Palmer & Ashby, 1992), MU studies have indicated that TMS is compatible with short latency facilitation by the fast corticospinal pathway which make monosynaptic connections with motoneurons (Brouwer & Ashby, 1990; Palmer & Ashby, 1992; Bawa & Lemon, 1993). However, TMS of the motor cortex can also produce disynaptic inhibition mediated by spinal Ia inhibitory interneurons (see Rothwell *et al.* 1991). Inhibition of muscle activity can occur following the facilitation produced by TMS (i.e. silent period, Calancie *et al.* 1987; Mills, 1988). Also, inhibition without muscle activity has been shown to occur with a stimulus intensity below the threshold for producing a muscle response in both proximal (Colebatch *et al.* 1990) and distal muscles (Davey *et al.* 1991).

TMS has also been used to determine the task related differences in corticospinal activation. Several lines of investigation suggest that the corticospinal neurons are preferentially involved in fine control of the digits. In human FDI, MEPs following TMS are larger during the performance of a precision grip when compared to a power grip (Datta *et al.* 1989; Schieppati *et al.* 1996), or to a simple index finger abduction task (Flament *et al.* 1993). Corticospinal excitability in humans has also been studied during various phases of a task requiring the subject to reach, grasp and lift an object using a precision grip (Lemon *et al.* 1995). The amplitudes of the corticospinal responses evoked by TMS showed a striking modulation during different phases of the task. The intrinsic hand muscles received the strongest cortical input as the digit closed around the object, and just after the subject first touched the object at the onset of manipulation. Given that no similar task-related variations in MEP amplitude occurs following TES (Datta *et al.* 1989; Schieppati *et al.* 1996) this suggests that it is a cortical mechanism which is responsible for the task related changes with TMS. This was confirmed directly by Baker *et al.* (1995) using TMS in an awake monkey performing a precision grip. During task performance, the identified corticospinal volley displayed a mean modulation of 13%, with the largest volley occurring during the hold phase of the task. No comparable modulation was observed in a volley evoked by electrical stimulation of the corticospinal fibres via chronically implanted electrodes in the cerebral peduncle. Therefore, changes in cortical excitability are the most likely mechanism for variations in the response to TMS.

Although the evidence presented above indicates that the corticospinal fibres are most excitable during finely controlled movements, there is limited evidence on the role of the corticospinal pathway and its plasticity during skill acquisition and performance of skilled tasks. The available evidence on this issue is presented in section 1.5.3.

1.3.3.5 Developmental studies.

Within a single species, further evidence relating the corticospinal tract to fine control of hands has been gained by observing the behavioural effects as the corticospinal connections are developing, or, by sectioning the pyramidal tract and preventing the normal connections

from forming. Lawrence & Hopkins (1976) sectioned the pyramidal tracts in infant monkeys within a few days of birth before significant development of the CM cell connections had occurred. These animals never gained the capacity for fractionated control of distally acting muscles or to learn a precision grip task, even though their general motor development proceeded normally.

The use of TMS of the cortex, in concert with the assessment of corticospinal terminations in the ventral horn of the spinal cord, has been helpful to assess the role of corticospinal connections in infants. In adult man and macaque monkey, TMS produces a short-latency excitation in the surface EMG of upper limb muscles, which has been shown to occur via the corticospinal pathway (Edgley *et al.* 1990; Palmer & Ashby, 1992). Flament *et al.* (1992) has shown in 2 to 3 month old monkeys that short-latency EMG responses to TMS were absent. Short-latency excitatory responses equivalent in amplitude and duration to adults were established in these monkeys when they were aged 6 to 8 months (Flament *et al.* 1992). In human infants, the latency and threshold for activation within the normal range are not obtained until around 18 months to 2 years (Eyre *et al.* 1991), which coincides with the capacity to produce fractionated control of the distal hand muscles.

Given that normal short-latency responses and independent finger movements occur in parallel, it would be of interest to relate this to the formation of corticospinal synapses with motoneurons during development. In newborn rhesus monkeys, no cortical fibres are distributed to the motoneuronal cell groups (Kuypers, 1962), and TMS produces almost no response (Flament *et al.* 1992). In the macaque monkey, no corticospinal projections to motoneurons appear until 6 to 8 months after birth (Kuypers, 1962), coinciding with the establishment of a short-latency excitation (similar to adults) after TMS (Flament *et al.* 1992). It seems apparent that corticospinal terminations to motoneurons increase in number during post-natal development which coincides with behavioural changes involving the use of distally acting muscles of the hand and fingers. Therefore, direct corticospinal connections appear to be essential for the performance, during development, of precisely controlled finger movements.

1.4 Motor unit synchronization

The wide divergence of inputs within a motoneuron pool of a single muscle has been extensively studied in humans through the recording of single MU discharge. Functional connections to motoneurons in the human motor system can be revealed through the analysis of the discharge of pairs of MUs on a spike-by-spike basis. This technique, which was first introduced by Buchthal & Madsen (1950), and is now known as cross-correlation (Moore *et al.* 1966), has shown that MUs have an increased tendency to fire within a few milliseconds of each other at greater than chance probability (Sears & Stagg, 1976). This phenomenon, termed MU short-term synchronization, is most prominent in distal muscles engaged in fine voluntary motor control such as the FDI (Datta *et al.* 1991; De Luca *et al.* 1993). Recently, evidence has been obtained to suggest that MU synchronization can be modified under certain behavioural conditions, with increases in MU synchronization obtained after strength training (Milner-Brown *et al.* 1975), modifications involved with constant preferential use of the hand (Schmied *et al.* 1994) and voluntary alterations in the relative proportions of common inputs via descending commands (Schmied *et al.* 1993). It is an aim of the present thesis to examine the strength of FDI MU short-term synchronization in individuals with different long-term patterns of muscle use, including individuals who have trained over many years for skill- or strength-related tasks. It is expected that long-term skill-training will have the greatest influence on MU synchronization in intrinsic hand muscles, as corticospinal inputs are known to be important for fine control of the digits and for MU synchronization.

1.4.1 Methods to detect synchronous activity within a muscle

Over the years, a number of different methods have been used to determine the existence of MU synchronization during voluntary contraction of a human muscle. Although each method provided limitations to the estimate of MU synchronization, some techniques proved more reliable and more reproducible than others. Earlier studies used visual inspection of the surface EMG signal (Adrian, 1947; Missiouro *et al.* 1962; Mori, 1973), but reliable

estimates of MU synchronization could not be inferred from this gross EMG. Further studies established that estimates of MU synchronization could not be obtained without the use of the firing times of at least one MU. Recent studies have either used the surface EMG signal in comparison with the MU firing times (Milner-Brown *et al.* 1975), or, the cross-correlation of the firing times of two MUs (Sears & Stagg, 1976), in order to assess the level of MU synchronization in human muscles.

1.4.1.1 The surface EMG technique

Milner-Brown *et al.* (1973a) were the first to measure the correlation between the activity in single MUs and that in the whole muscle as recorded by the surface EMG. This consisted of averaging the rectified and unrectified surface EMG with respect to the discharge of a reference MU recorded by an intramuscular electrode within FDI. The unrectified surface EMG average represents the contribution from the reference MU to the surface EMG, because the contribution of the positive and negative waveforms of other MUs not synchronized to the reference MU average to zero. This cancellation is avoided when taking the rectified average. The rectified surface EMG comprises the waveform of the reference unit after rectification, an average EMG level (baseline) due to independent firing of other MUs, the contribution of other MUs that are synchronized to the reference MU, and an artifact associated with the signal rectification process. The advantage of this technique over the early surface EMG methods is that it estimates MU synchronization from the discharge of a single MU, which improves the reliability of the measure. It also has the advantage of simply and quickly quantifying the strength of MU synchronization for each reference MU with a number of other MUs (see Chapter 5 for details). However, limitations of this method are consistent with all estimates involving the use of the surface EMG signal, in that the contribution of single MUs to the surface EMG are not constant, and variations in the contribution of single MUs to the surface EMG with time are not necessarily correlated with a change in MU synchronization.

In the original investigation, Milner-Brown *et al.* (1973a) recognised that the rectification artifact and the amount of MU synchronization varied with the signal-to-noise ratio, and they

used a theoretical approach to calculate this contribution. When subtracting the rectification artifact, the surface EMG technique has been shown to provide a sensitive measure of the level of MU synchronization within a population of neurons (Roscoe *et al.* 1985). However, due to the extra data processing required to calculate the rectification artifact, Milner-Brown *et al.* (1975) chose to simplify the method by assuming that the rectification artifact was fixed, and was independent of the signal-to-noise ratio. Using the simplified method, Milner-Brown *et al.* (1975) reported that FDI MU synchrony was two to three times stronger in weight-lifters than in untrained subjects. These observations have been highly influential in the literature as evidence for a training-related neural adaptation. However, when using this method, Yue *et al.* (1995) have recently reported that the contribution of the rectification artifact to the amount of synchronization varies non-linearly with the signal-to-noise ratio. This result indicates the need to maintain similar contraction levels when using the surface EMG method across conditions (e.g. pre- and post-training; Milner-Brown *et al.* 1975). If the contraction levels differ in a consistent manner, then a change in the strength of synchrony using this index may simply be due to differences in the number of active MUs. For this reason, a more reliable method (such as the cross-correlation of MU discharges; see below) has been used in Chapter 4 to compare the strength of MU synchronization in strength-trained and untrained subjects in an attempt to verify the findings of Milner-Brown *et al.* (1975).

A further aim of this thesis was to compare the surface EMG and cross-correlation procedures, as there is currently no direct evidence that the two methods are equivalent. It is generally accepted that cross-correlation of MU discharge times is a reliable estimate of the overall extent of MU synchronization in a muscle provided that trials of long duration are used and many MUs are examined within a single experiment. However, it is not always possible to satisfy these criteria under experimental conditions. The advantage of the surface EMG technique over cross-correlation of discharge times is that it estimates MU synchronization between the reference MU and a population of MUs in a single measure, and only one, or a few reference MUs are required for the analysis. Although the simplified surface EMG method is a less direct measure of MU synchrony than cross-correlation, it is

unknown whether the simplified surface EMG method gives a reliable, overall impression of MU short-term synchronization in a muscle which is equivalent to that obtained with cross-correlation of a large sample of MU pairs. It is also unclear whether the two methods are measuring the same physiological processes; for example, whether the extent of short-term synchrony is similar when calculated with each method. For these reasons, a comparison has been made between the estimate of MU synchrony using the two methods in the same MUs (Chapter 5). A comparison between both methods would determine whether the cross-correlation procedure (which is technically more difficult) is necessary to accurately estimate MU synchrony, rather than the simplified surface EMG method. Results from the analysis in Chapter 5 indicate that estimates of the strength of MU synchronization using the surface EMG and cross-correlation procedures are not equivalent. This finding, combined with the finding that the surface EMG method is sensitive to the signal-to-noise ratio (Yue *et al.* 1995), casts some doubt on the use of the surface EMG method for quantitative measurement of MU synchrony.

1.4.1.2 Cross-correlation of motor unit action potentials

Buchthal & Madsen (1950) were the first to apply a form of cross-correlation analysis to determine a degree of MU synchronization in excess of chance. This technique used a method of mechanically counting action potentials of single MUs from two separate electrodes based on their firing times. Two impulses were considered coincident if the spikes discharged within a limited time interval. Random coincidences were estimated based on the pulse duration of each spike and the firing frequency of each MU. Improvements to this technique were made by Bigland & Lippold (1954), who used a similar method of manually counting action potentials, but in this instance, the MUs were recognised on the basis of waveform shape, size and regularity of repetition.

A major refinement of the earlier cross-correlation techniques involved a more objective assessment of MU firing times (Person & Mishin, 1964; Moore *et al.* 1966). The times of occurrence of spikes from two MUs were used to construct a histogram in which the discharge times of the reference spike, defined as time zero, were correlated with those of the

other spike train, termed the event MU. If a tendency towards synchronization exists, there will be a peak in the cross-correlation histogram around the time of firing of the reference MU (Moore *et al.* 1966). The appearance of peaks and troughs in the histogram indicate a raising or lowering of the probability of MU discharge, brought about by direct synaptic communication between the cells or through a common pre-synaptic input to the neurons (see section 1.4.2. for details). The cross-correlation procedure has become the most widely used method of determining the interdependence of human MU discharges, and MU short-term synchronization has been established in human hand (Milner-Brown *et al.* 1975; Datta & Stephens, 1990; Bremner *et al.* 1991a; Bremner *et al.* 1991b; Nordstrom *et al.* 1992), forearm (Schmied *et al.* 1993; Schmied *et al.* 1994), leg (Dietz *et al.* 1976; Baker *et al.* 1992; Davey *et al.* 1993; Nielsen & Kagamihara, 1994), neck (Adams *et al.* 1989), and jaw (Nordstrom *et al.* 1990) muscles. MU synchronization has also been investigated in different muscles in the same subject (Bremner *et al.* 1991a; Bremner *et al.* 1991b), in the same subject during different tasks, and in different muscles during different tasks (Bremner *et al.* 1991c). A number of reports have indicated changes in the level of MU synchronization under various conditions, including fatigue (Buchthal & Madsen, 1950), tremor (Dietz *et al.* 1976; Logigian *et al.* 1988), reflex compared to voluntary activation (Adams *et al.* 1989), during various types of pathological states involving motor dysfunction (Davey *et al.* 1990; Datta *et al.* 1991; Baker *et al.* 1992; Farmer *et al.* 1993b), and even with pharmacological intervention (Logigian *et al.* 1988).

1.4.2 The mechanism of motor unit synchronization.

It is now well accepted that MUs discharge within a few milliseconds of each other more often than expected by chance. The mechanism of this synchronous activity has been a topic of intense debate over a number of years. Generally, the most widely accepted view is that MU "short-term" synchronization (Sears & Stagg, 1976) arises from shared inputs from branched axons of single last-order neurons that increase the probability of simultaneous discharge in the target neurons sharing these inputs (Kirkwood & Sears, 1982; Datta & Stephens, 1990). Therefore, MU synchronization reveals details of the distribution of

shared, branched-axon inputs to the motoneurons at the spinal level (Moore *et al.* 1970).

Sears & Stagg (1976) were first to put forward the hypothesis that the joint occurrence of unitary EPSPs evoked in motoneurons by branches of common stem pre-synaptic neurons would produce short-term synchronization of their discharges. Using cross-correlation to detect synchronized firing, Sears & Stagg (1976) tested the hypothesis among groups of intercostal motoneurons in the anaesthetised cat discharging in response to their natural synaptic drives. From the cross-correlograms, they found a narrow central peak extending to ± 3 ms, indicative of "short-term" synchronization due to the common pre-synaptic connectivity.

Subsequently, Kirkwood & Sears (1978) obtained support for this hypothesis by showing that equations developed from a model of the branched stem hypothesis fitted the time course of synchronization of cat intercostal motoneuron firing. According to this analysis, the time course of short-term synchronization of firing between two motoneurons may be calculated given the time course of the unitary EPSPs evoked by branches of common stem pre-synaptic fibres and the relationship between EPSP time course and the time course of the raised probability of firing produced by each motoneuron (Kirkwood & Sears, 1978). This idea, first shown for intercostal motoneurons in the cat, was later adapted for data from human MUs in man (Datta & Stephens, 1990). From this data, short-term synchrony in humans is generally considered to occur with a peak width less than 15 ms.

Although the underlying EPSPs may explain small variations in the time-course and amplitude of MU synchronization, the extremely large variations in the duration of the central cross-correlation peak observed in animal experiments (Kirkwood *et al.* 1982; Kirkwood *et al.* 1984) and some human experiments (Davey *et al.* 1990; Datta *et al.* 1991; Baker *et al.* 1992; Farmer *et al.* 1993b) indicates that additional mechanisms must be taken into account. From the equations of Kirkwood & Sears (1978) only the narrowest central peaks of synchronization can be regarded as being caused exclusively by a common branched-axon pre-synaptic input. For peaks with broader durations, synchronization of separate pre-synaptic inputs to the motoneurons (broad duration synchronization) must be considered

(Kirkwood *et al.* 1982; Kirkwood *et al.* 1984).

1.4.3 The origin of the common pre-synaptic input

Two experimental observations support the view that the muscle spindle Ia afferent is unlikely to be an important contributor to the generation of MU synchronization. First, it has been demonstrated that short term synchronization is present in a patient with a post-infective sensory neuropathy which led to the functional loss of large myelinated peripheral afferents below the neck (Baker *et al.* 1988). Second, Bremner & Baker (1990) have shown that vigorous vibration of an intrinsic hand muscle (which activates muscle spindle afferents) has no effect on the strength of MU synchronization.

In contrast, two characteristics related to the nature of corticospinal neurons suggest that they are the most likely input responsible for synchronous MU discharge. These characteristics are; 1) the wide divergence of corticospinal inputs within and between motoneuron pools, and 2) the relative number of corticospinal projections to different motoneuron pools.

Using anatomical techniques, substantial intraspinal branching of corticospinal axons has been observed by Shinoda *et al.* (1979). It has also been shown through retrograde labelling techniques in the monkey that some corticospinal axons give off collaterals which make direct contact with dendrites of other motoneuron pools (Shinoda *et al.* 1981). The branching of CM cells within a muscle can also be determined using STA (see section 1.3.3.4 for details). These STA studies have indicated that CM cells branch to innervate many (if not all) of the motoneurons of a muscle's motoneuron pool (Fetz & Cheney, 1980; Buys *et al.* 1986; Mantel & Lemon, 1987). Other estimates have suggested that single motor cortical cells in primates may facilitate up to 75% of motoneurons in their target muscles (Asanuma *et al.* 1979). The STA technique has also been used to demonstrate that single corticospinal fibres can excite motoneurons supplying different groups of muscles in the monkey. From the study of the discharge of single corticospinal fibres during wrist flexion and extension, Fetz & Cheney (1980) found that each CM cell contacted a mean of 2.4 forearm muscles. The wide divergence of corticospinal inputs both within and between

motoneuron pools would allow a single CM cell to exert a nearly simultaneous excitatory influence over many different motoneurons and thus cause synchronization of their discharges.

From the studies which have assessed the strength of MU synchronization in different muscles (Bremner *et al.* 1991a; Bremner *et al.* 1991b; De Luca *et al.* 1993), it has become apparent that the common stem pre-synaptic fibres are more effective in distal muscles than in more proximal muscles. In contrast to Ia afferents, the CM neurons of the pyramidal tract are known to have powerful monosynaptic connections with motoneurons of intrinsic hand muscles (Clough *et al.* 1968). Therefore, the significant branching of corticospinal axons, and the finding that they are more effective to intrinsic hand muscles than other muscles, seems to be consistent with the levels of MU synchronization displayed in cross-correlograms of various human muscles (De Luca *et al.* 1993).

Supporting evidence for the cortical origin of the common pre-synaptic neurons producing short-term synchrony has come from experimental studies in animals and humans which have observed MU synchronization under abnormal conditions, especially once the cortical influence has been altered or removed. In early studies on MU synchronization in cat intercostal muscles, the effects of acute and chronic central nervous lesions on the time course of MU synchronization have been described (Kirkwood *et al.* 1982; Kirkwood *et al.* 1984). These studies have indicated that spinal cord lesions promoted broader, and much stronger MU synchronization in the anaesthetised cat.

In humans, short-term synchrony has been assessed in the extensor digitorum communis (EDC) and in the tibialis anterior (TA) muscles in paraplegic patients (Davey *et al.* 1990). All of the patients had sustained injury to their spinal cord above the level of segment L4 (the level innervating the TA) but below the level of C7 (innervating the EDC). It was established that there was little difference in the strength of short-term synchronization in EDC between paraplegic and normal subjects. In contrast, short-term synchronization was extremely weak in the TA of the paraplegic group compared to the TA of normal subjects.

Several other clinical observations in humans favour the contribution of supraspinal centres in the synchronization of MU discharges during voluntary contraction. Patients with clinically identified central lesions following strokes display a broader duration MU synchronization compared to that found in normal subjects (Datta *et al.* 1991; Farmer *et al.* 1993b). Broad duration synchronization in FDI was also found in a patient with a rostral cervical spinal lesion but not in a patient with a caudal (thoracic) spinal lesion (Datta *et al.* 1991). Also, the strength of MU synchronization has been examined in patients with diseases which principally affect the corticospinal pathway (Schmied *et al.* 1994). In four patients with amytrophic lateral sclerosis and one patient with primary lateral sclerosis, almost no MU synchronization could be detected in the dominant extensor carpi radialis (ECR) muscle compared to strong MU synchronization in the ECR of age-matched controls, which is persuasive evidence favouring the corticospinal involvement in MU synchronization.

The most convincing evidence of the source of the inputs controlling intrinsic hand muscles can be obtained from patients with congenital mirror movements. This phenomenon is characterised by an involuntary movement of a muscle in one hand due to the voluntary activation of the homologous muscle in the contralateral hand (Schott & Wyke, 1977; Schott & Wyke, 1981). In a Klippel-Feil patient who displayed such mirror movements, Farmer *et al.* (1990) established that TMS over either hemisphere elicited bilateral and symmetrical short-latency muscle responses in intrinsic hand muscles. Following cutaneous stimulation of the digital nerves of the index finger, short-latency (spinal) reflex responses occurred on the stimulated side only, while the longer latency (presumed transcortical) responses, of approximately equal size and latency, were distributed bilaterally (Farmer *et al.* 1990). When using cross-correlation analysis of individual MU discharges from both hands (one MU in FDI of each hand), the cross-correlation histogram revealed a central synchronous peak similar to that observed when two MUs are cross-correlated from the same hand. This is never seen in normal subjects. This information indicates that the mirror movements in the patient with Klippel-Feil syndrome were the result of abnormally branched fast-conducting corticospinal tract fibres which project to motoneuron pools on both sides of the spinal cord.

The abnormal pattern of MU synchrony strongly implicates branched corticospinal axons as an important source of MU short-term synchronization.

Recently, the frequency domain equivalent of cross-correlation analysis has been applied to human MU studies in an attempt to detect periodic firing of common inputs to motoneurons (Farmer *et al.* 1993a; Mills & Schubert, 1995). These studies have revealed that coherence can be detected between pairs of MUs in FDI in the frequency ranges 1-12 Hz and 16-32 Hz during voluntary isometric abduction of the index finger. The finding of significant coherence between MU pairs at these frequencies implies some common periodicity of the presynaptic input (see Farmer *et al.* 1996). Particular emphasis has been placed on the frequency range 16-32 Hz, as this represents the common modulation of inputs to motoneurons which could not be due to the intrinsic properties of motoneuron firing, which generally occurs between 6-12 Hz. Farmer *et al.* (1993a) established that the behaviour of the pre-synaptic pathways that produce MU short-term synchronization were similar to the pathways which were responsible for the 16-32 Hz coherence. Based on arguments similar to that obtained for MU short-term synchronization (Datta *et al.* 1991; Farmer *et al.* 1993b), they confirmed that the pathway responsible for the 16-32 Hz coherence resulted from activity at these frequencies in central motor pathways, including the corticospinal tract (Farmer *et al.* 1993a).

Although there is a wealth of evidence suggesting that the corticospinal pathway is involved in the production of MU short-term synchronization, recent evidence casts some doubt on the contribution of CM projections to MU short-term synchronization. Mills & Schubert (1995) examined the effect of TMS on MU short-term synchronization in human FDI muscle. They found that TMS, which activates fast corticospinal fibres, did not effect the size of the central cross-correlogram peak of a MU pair. It was concluded from this work that the fast corticospinal fibres activated by TMS provide relatively independent inputs to motoneurons. This puzzling result suggests either 1) CM projections do not contribute to MU synchronization, or 2) there may be a separate subset of CM cells, the fastest of which are activated by TMS and provide independent inputs to motoneurons, and the slower CM

cells have a much wider divergence to the motoneuron pool and are responsible for MU short-term synchronization. To date, this latter option remains unexplored.

In summary, the inputs responsible for the generation of MU short-term synchronization are from predominantly supraspinal sources. From both time- and frequency domain analyses, evidence has accumulated regarding the corticospinal origin of MU synchronization. It is suggested that descending pathways of cortical origin, including branched stem CM axons, are likely to be important in the generation of short-term synchronization, although some evidence refutes this claim. Irrespective of this, only the narrowest of cross-correlogram peaks would be caused exclusively from common CM cell inputs, and synchronization of separate presynaptic inputs should be considered as contributing to peaks with broader duration's commonly observed in cross-correlograms of human MU discharge.

1.4.4 Common drive of motor units and motor unit synchronization

During voluntary activation, mean firing rates of active MUs are modulated in parallel, a phenomenon that has been termed common drive (De Luca *et al.* 1982b). The existence of common drive indicates that the nervous system does not control the firing rates of MUs individually, but acts on the motoneuron pool in a uniform fashion. The analysis of common drive is based on trends in smoothed MU firing rates (De Luca *et al.* 1982b), and is thus distinct from MU short-term synchronization, which is based on discrete discharge times. It is the direct corticospinal inputs which are believed to be the major input involved in the generation of MU short-term synchronization (Datta *et al.* 1991; Farmer *et al.* 1993b). Due to the wide divergence of corticospinal fibres (see section 1.4.3), the corticospinal pathway (including CM and non-CM components) provides inputs which could be responsible for the common modulation of MU firing rates. Other inputs with well characterised connectivity which could be responsible for the common modulation of firing rates are the muscle spindle Ia afferents (see below).

The source of inputs controlling the common fluctuations in mean MU discharge rates has never been elucidated experimentally. De Luca *et al.* (1982b) have postulated that the source

of common drive could be central as well as peripheral. Considerable importance has been placed on peripheral afferent inputs in providing the common drive behaviour of the motoneuron pool. Common drive analysis on a muscle with no muscle spindles, the orbicularis oris of the lower lip, revealed common drive cross-correlation levels similar to other muscles containing spindles (Kamen & De Luca, 1992). Furthermore, it is understood that muscle spindle activity is minimal under isometric conditions, which is the condition of activation from which most common drive analyses have been derived. These findings suggest muscle spindle inputs are not an important source of the common fluctuation in MU firing rates, at least under these experimental conditions.

Empirical evidence for a central origin of common drive comes from the analysis of common drive and its relationship to handedness in human FDI (Kamen *et al.* 1992). In this study, common drive was stronger in the dominant hand for both right-handed (RH) and left-handed (LH) subjects. It is possible that these differences might be attributable to differences in the organisation of peripheral receptors between the dominant and non-dominant limb, however, a number of studies have indicated that there are no left-right differences in the density of muscle spindles (Barker & Chin, 1960; Buxton & Peck, 1990), and efforts to demonstrate asymmetry in the conduction velocities of peripheral nerves have produced ambiguous results (Trojaborg, 1964; Tan, 1985b). In contrast, supporting evidence exists for a supra-segmental component to left-right differences in synaptic inputs to motoneurons, as there are more pyramidal tract fibres directed to the right than to the left hand in about 80% of human brains (Yakovlev & Rakic, 1966), and in relation to H-reflex studies, weak voluntary contraction introducing supraspinal influences on spinal circuits produces a facilitation of the H-reflex that is greater on the dominant side (Tan, 1989a).

Although the source of the modulation for common drive has not been identified, its 1-2 Hz modulation frequency may reflect the activity of common inputs to motoneurons. It could also arise from common modulation of input neurons that project with minimal divergence to different motoneurons within the pool, and so would not give rise to short-term synchronization. It has been suggested that the analysis of MU synchronization during co-

contraction of opposing muscles of the thumb (flexor pollucis longus and extensor pollucis longus) have shown no consistent MU synchronization, although strong common drive has been detected (De Luca, 1985). At present, there are no published studies in which common drive and short-term synchronization analyses have been performed on the same set of data, so as to explore a relationship between them. As MU short-term synchronization is likely to be attributed to common-stem pre-synaptic inputs from single CM cells (Datta & Stephens, 1990; Farmer *et al.* 1993a), the relationship between synchrony and common drive in the same MU pairs would provide an indicator of the influence of CM cells on the common modulation of firing rates during an isometric contraction. This analysis has been undertaken in Chapter 3.

1.5 Neural adaptations to various muscle usage patterns

Although CNS adaptations are believed to underly the learning of a motor task, relatively little insight has been gained as to the precise location and mechanisms which are responsible for an improvement in performance. This is because the repetitive learning and acquisition of new skills involves dynamic changes within the nervous system which may be widely distributed. Also, the altered physical activity is likely to involve functional, and perhaps structural changes at all levels of the motor pathway, which is often extremely inaccessible, particularly in humans. Despite these difficulties, the examination of the acute CNS plasticity that occurs during recovery after trauma, (such as that which occurs after stroke or amputation) have revealed that the cortical maps in a range of mammalian species have the potential to reorganise, even in mature nervous systems (see McComas, 1994 for a review). This is important to establish, as it has implications for other forms of neural plasticity, such as that resulting from different training regimes which result in an improvement in performance. However, changes which result from selectively increased activity are not as dramatic as those in stroke or amputation, which makes it difficult to detect any neural reorganisation which may occur as a result of short-term training procedures. As a compromise, many studies have attempted to investigate the neural adaptations as a result of

long-term training. These include the habitual use of a hand during skilled tasks which are encountered in everyday life, or the long-term adaptations resulting from training for a particular task. These are the conditions under which the present series of investigations have been undertaken. If training related differences in the neural control strategies can be detected in individuals who have differing patterns of long-term muscle use, then this would prompt further studies of the neural adaptations induced by short-term training regimes.

1.5.1 Handedness

When asked to perform a skilled task such as writing, only about 8% of the human population prefer to use their left hand, and the remainder use their right hand (Halpern & Coren, 1990). Although numerous explanations have been proposed to account for this small proportion of left handers in the population, there does not appear to be a widely accepted view, and the issue is still unresolved. Current theories concerning the aetiology of handedness can be grouped into three categories: genetic, environmental-cultural, and environmental-prenatal. The three categories are not necessarily mutually exclusive, and possibly parts of all three may contribute to the determination of handedness.

Evidence for a genetic basis for handedness comes from investigations dealing with the incidence of left-handedness in adoptive families. Carter-Saltzman (1980) showed that, in contrast to that of normal, biological children, the handedness of children adopted in the first year of life showed no relationship to that of their adoptive parents. This evidence suggests that familial trends for handedness are reflecting genetic effects. The most detailed studies attempting to explain a genetic component of handedness has been performed by Annett (see Annett, 1996). This author has suggested that the majority of persons in the population carry a 'right-shift' gene which increases the probability of left-hemisphere dominance for controlling function. However, approximately 18% of the population have random dominance for handedness, and accidental factors (such as prenatal influences; see below) determine the lateralisation of handedness for that segment of the population. Based on this theory, no purely genetic influence could account for the determination of handedness.

The premise of the environmental-cultural influence on hand preference is that handedness is a learned phenomenon that is passed on through generations. Under experimental conditions, evidence exists indicating that hand preference can be altered by learned environmental factors (Collins, 1975), although the degree to which this occurs due to normal environmental pressures is unclear (see Schwartz, 1990). The findings of reduced frequency of occurrence of left-handedness with age have been interpreted as reflecting pressure to conform to a RH environment (see Porac *et al.* 1980). However, a recent survey of the literature reports that the percentage of adult left-handers has not significantly changed in 80 years (Halpern & Coren, 1988). In addition to no significant change in reported incidence of left-handedness, research has shown that it is extremely difficult to successfully change preferred hand use. Porac *et al.* (1986) found that a high proportion of initially LH individuals had been subjected to direct pressures (from parents, teachers and others) to shift to right-handedness. Their subjects reported a successful shift rate of only 29% for males and 62% for females, which would account for only a small proportion (~4%) of the total population shift from LH to RH (see Halpern & Coren, 1990).

Finally, the unusually high incidence of left-handedness in selected clinical populations has led researchers to suspect that left-handedness is sometimes pathological in origin. A vast volume of literature has suggested that left-handedness may be a marker for the presence of some form of neuropathological insult as a result of prenatal or birth-related complications (see Halpern & Coren, 1990). It has been argued that prenatal stress causes left cerebral motor damage resulting in a 'weakness' of the right hand, prompting a shift to left hand use (Bakan, 1971). Although the existence of pathological handedness is not denied, there is a long list of studies which do not support this extreme view (Schwartz, 1990). The accumulated data appear to support the contention that the majority of left-handers in the population are present due to what is considered normal genetic variability, *and* prenatal environmental influences. The actual numbers of left-handers in the general population is higher than the genetic component would warrant because 'pathological' individuals, as a result of cerebral insult to certain motor areas, become LH.

There is currently a growing body of evidence suggesting that left handers show smaller between-hand differences than right handers. When hand grip strength is measured, right handers have a stronger right hand, whereas left handers show no significant differences between the two hands (Peters & Servos, 1989). A similar finding has been established for throwing accuracy (Peters, 1990). Perhaps the greatest lateral differences between left and right handers has been observed during tasks involving skilled digits use, where the rapid and selective use of individual digits depends exclusively on corticospinal fibres with direct projections onto motoneurons (see section 1.3). These tests of hand skill, such as hand writing, finger tapping speed and pegboard tasks, indicate that right handers show large differences in skill between dominant and non-dominant hands, which is not observed in left handers (Peters & Servos, 1989; Peters, 1990; Provins & Magliaro, 1993).

Although most individuals have a tendency to use one hand in preference to the other during everyday tasks, evidence exists suggesting that the preferred hand does not always produce the best performance. For example, Kimura & Vanderwolf (1970) have investigated the relationship between hand preference and the performance of individual finger movements in left and right hands. During isolated flexion of a sequence of single digits, they found that right handers performed the task better with their non-preferred hand. Similarly, Carey *et al.* (1994) examined index finger movement tracking scores and found that subjects were more accurate at tracking with their non-dominant hand compared to the dominant hand. However, when considering the results of these studies it is important to distinguish between skilled and independent movements. A skilled movement requires fractionated and fine control of individual muscles which need to be coordinated with synergists and antagonists. These are the movements which are usually performed during everyday tasks such as handwriting. In contrast, independent movements require isolation of the muscles controlling the movement, which are usually restricted to experimental studies of this type. It is in practiced skilled tasks such as handwriting where significant performance advantages are observed with the dominant hand in RH subjects (Provins & Magliaro, 1993).

Anatomical evidence suggests that there are structural differences between sides which may

account for the skill differences between right and left hands. When considering pyramidal tract anatomy in man, Yakovlev & Rakic (1966) have demonstrated that more fibres project from the left motor cortex to the right side of the body in about 80% of individuals. To support this view, Nathan *et al.* (1990) has shown in man that the corticospinal tract is larger on the right side of the body in 75% of cases. A larger lateral corticospinal tract on the right side would indicate a right-sided preference in most individuals, but does not preclude a high degree of motor skill on the left side. The relation between hand preference and the larger pyramidal tract on the right side is not very well understood. For example, it is not known what proportion of the pyramidal fibres are CM projections, which provide the neural substrate for skilled movement of the digits. Also, Kertesz & Geschwind (1971) observed that the pattern of crossover of the pyramidal tracts which was characteristic of right handers (left-sided tract crossing over before right-sided tract) was observed in all of their left handers, suggesting that the pattern of crossover is not related to handedness.

Examination of the relationship between hand preference and physiological asymmetries of the brain have revealed left-right differences in the organisation and effectiveness of the corticospinal pathway. Nudo *et al.* (1992) has recently shown that the sensorimotor representation of the dominant hand in monkeys occupies a larger area of the motor cortex than that of the non-dominant hand. This difference was related to the hand preference of the individual animals in a task requiring skilled digit use. Using TMS in humans, Wasserman *et al.* (1992) found that the dominant abductor pollicis brevis (APB) muscle tended to have a larger cortical representation than the non-dominant APB. In addition, the threshold for MEPs in the resting APB following TMS of the motor cortex is lowest for the preferred hand in both LH and RH subjects (Triggs *et al.* 1994). Larger differences in the muscle activation threshold between sides were observed in RH subjects, and in those with the most pronounced lateralisation in hand preference (assessed by questionnaire).

Other neurophysiological studies have provided evidence for left-right differences in the function of the human nervous system. Using the H-reflex technique, the excitability of motoneurons innervating upper limb muscles has been shown to be higher on the preferred

than the non-preferred side (Tan, 1989a; Tan, 1989b). However, lateralised spinal differences in lower limb muscles are less clear. Some investigators have found no consistent relationship between spinal excitability and lateral dominance in soleus and gastrocnemius muscles (Goode *et al.* 1980; Nativ & Allard, 1989) while others have reported an inverse relationship (Tan, 1985a). The inconclusive nature of these results may be due to the insensitivity of the H-reflex technique to accurately assess minute handedness-related differences in spinal excitability, or a failure to use detailed questionnaires or tests of hand skill to assess the full spectrum of handedness in the subjects examined.

Further evidence for handedness-related differences in neuronal excitability has come from the assessment of MU synchronization in dominant and non-dominant arms. Schmied *et al.* (1994) found that the strength of MU synchrony in ECR MUs was higher in the preferred arm in both LH and RH subjects. As common branched axons from direct corticospinal fibres are likely to be important for MU synchronization (see section 1.4), this suggests a stronger net input from branched CM cells to motoneurons controlling muscles acting on the wrist of the preferred arm. This stronger input presumably reflects differences in the discharge rate, projection frequency or synaptic efficacy of the direct corticospinal inputs controlling the preferred and non-preferred arm.

One aim of the present series of investigations was to examine the differences in MU discharge properties (MU discharge rate, regularity, synchronization) in an intrinsic hand muscle (FDI) in dominant and non-dominant hands (Chapter 2). The initial hypothesis was that the strength of MU synchronization would be greater in the FDI of the dominant hand during isometric abduction of the index finger. This was based on evidence that there are more corticospinal fibres directed to the right side in most human brains (Nathan *et al.* 1990), the threshold for TMS activation of a hand muscle is lower on the dominant side (Triggs *et al.* 1994) and the motor cortical representation in the hemisphere controlling the dominant hand is larger during index finger abduction as revealed by magnetoencephalography (Volkmann *et al.* 1996). The strongest evidence comes from the finding that the strength of MU synchronization in the wrist extensor, ECR is higher in the

preferred arm (Schmied *et al.* 1994). Assuming no differences in divergence of corticospinal axons within the motoneuron pool or efficacy of corticospinal inputs to dominant and non-dominant hands, it would be expected that the strength of MU synchronization would be higher in dominant hand muscles. However, the facility of fractionated muscle activation provided by the corticospinal inputs is a fundamental difference in muscles controlling the digits compared to forearm muscles acting on the wrist such as ECR, where the requirements for fractionated control of individual muscles is less critical. Handedness related differences in direct corticospinal inputs (as measured by MU synchronization) in muscles requiring fine control (such as FDI) have not been established experimentally, and this was the topic of investigation in Chapter 2.

However, the results obtained in Chapter 2 did not match the initial hypothesis, as the strength of MU synchronization was found to be lower in the FDI of the dominant hand of untrained RH subjects. This finding led to the formulation of two new hypotheses to explain this result; 1) individual CM cells have monosynaptic connections with a smaller proportion of motoneurons within the FDI motor pool in the dominant hand of RH subjects, or 2) CM cells were less active when the task was performed by the dominant hand. In Chapter 6, the latter hypothesis was tested by more direct methods. TMS and TES (which activate the corticospinal pathway at different sites) were used to examine motor cortex excitability in dominant and non-dominant hands during task performance. The MEP following TMS includes a component due to cortical excitability, which is not observed following TES. TMS has been used to show lateral differences in corticospinal excitability (Triggs *et al.* 1994) with the muscles relaxed. However, it is well known that the MEP has different characteristics in the relaxed and contracted muscle (Rothwell *et al.* 1987; Wilson *et al.* 1995). As task related differences in corticospinal effectiveness have been established for precision and power tasks using TMS (Datta *et al.* 1989; Flament *et al.* 1993; Schieppati *et al.* 1996), it seems reasonable to hypothesise that skill-differences in dominant and non-dominant hands would accentuate these task-related effects. As MU synchronization is likely to result from activity in branched corticospinal axons, and the strength of MU synchronization is lower in the dominant hand of RH subjects during index finger abduction,

the above evidence points to a reduced activity of CM cells controlling the dominant hand compared to the non-dominant hand during index finger abduction, which would result in a smaller MEP following TMS in the dominant hand compared to the non-dominant hand during the same task. This hypothesis has been tested in the present investigations by comparing the MEPs in FDI following TMS and TES during different levels of muscle activation (Chapter 6).

1.5.2 Skill-training

The nature of the neural adaptations at a spinal or cortical level that occurs when learning a highly specialised motor skill are poorly understood. This has been due to the difficulty in establishing a method to detect what may be minute neural modifications distributed over large neural networks which may occur during training, and the difficulty in implementing a highly skilled training regimen, particularly in animals. Irrespective of these difficulties, a number of studies indicate that training for a highly specialised skill can result in neural alterations that lead to behavioural gains.

Recently, a growing number of reports in animals indicate significant neural reorganisation in somatosensory areas as a result of training. Stimulation of a restricted skin surface in a finger pad of adult monkeys leads to an enlargement of its somatosensory cortical representation (Jenkins *et al.* 1990a). In adult cats, Recanzone *et al* (1990) reported that a single session of 6-8 hours of electrical stimulation of a cutaneous nerve is rapidly followed by an expansion of the cortical representation of that nerve. Finally, after periods of stimulation of pairs of vibrissae in rats, neurons in the primary somatosensory cortex enlarge their receptive fields to include both whiskers (Delacour *et al.* 1987).

There is also evidence to suggest motor cortex reorganisation as a result of training for a skilled task. In the rodent, the motor cortical representation of a body part expands after selectively increased activity (Humphrey *et al.* 1990). When monkeys are trained to keep contact with a rotating disk with one or two digits, there is evidence for a cortical expansion of the representation of those digits (Jenkins *et al.* 1990b). It has also been demonstrated

after differential training of the two forelimbs that larger dendritic fields are evident in motor cortex opposite the highly trained limb (Greenough *et al.* 1985). In the most comprehensive study on this issue to date, Nudo *et al.* (1996) reported that monkeys trained to perform skilled movements of the digits showed progressive and reversible changes in the motor cortical representations of the digits involved in the task. Upon cessation of training, these changes were shown to exist for at least several days after the acquisition of the new skill. These results support the view that the neural alterations as a result of different and special use when training can be observed in the somatosensory and motor cortical areas in adult animals.

In humans, limited information exists regarding the nature of neural adaptations which occur as a result of learning a highly specialised skill. The evidence which does exists relies on the use of indirect measures to infer adaptations within the nervous system as a result of training. In classical ballet dancers, Goode & Van Hoeven (1982) have shown that a change in the lower limb stretch reflex occurs gradually in the course of ballet training and correlates with the duration and intensity of training. Using in-vivo magnetic resonance morphometry, Schlaug *et al* (1995) have demonstrated a larger midsagittal area of the corpus callosum in professional musicians compared to age-, sex- and handedness-matched untrained subjects. They suggested that this difference was due to the larger anterior corpus callosum in the subgroup of musicians who had begun musical training at a young age, and reflected a difference in interhemispheric communication and possibly in hemispheric asymmetry of sensorimotor areas in musicians. These results have generally been interpreted as evidence for nervous system adaptation during the learning of skilled tasks in humans.

As it is the direct projection from the corticospinal tract to upper limb motoneurons which is important for fine control of the digits (section 1.3.3), it seems likely then, that neural adaptations as a result of the learning of a task requiring fine control would include alterations in corticospinal neuron activity. The most conclusive finding to support this view is from the study of the motor cortical outputs to the reading hand of Braille readers (Pascual-Leone *et al.* 1993). The authors demonstrated that the learning of this highly

specialised sensorimotor skill can increase the motor cortical representation of muscles in the reading finger at the expense of the representation of other fingers (Pascual-Leone *et al.* 1993). There is also evidence that the forced increased specialised use of a finger in Braille readers can lead to identifiable changes in the cortical somatosensory representation of the reading finger (Pascual-Leone & Torres, 1993). In contrast to these findings, preliminary evidence exists indicating that the motor cortical representation of thenar muscles following TMS is much smaller in a "world class" violinist compared to untrained individuals (Mortifee *et al.* 1994).

Although limited information exists, it is likely that the learning of a highly specialised skill results in changes in the corticospinal pathway affecting intrinsic hand muscles when skilled tasks are required to be performed. It may also influence the strategy used to perform less demanding tasks. It is an aim of the present series of experiments to investigate this idea further, by examining the role of corticospinal inputs to intrinsic hand muscles in individuals who have trained their muscles to play a musical instrument (Chapter 4). This will be achieved by assessing the strength of MU synchronization in dominant and non-dominant hands of individuals who are proficient at playing a musical instrument which requires precisely controlled independent use of the digits, such as playing the piano. By assessing MU synchronization in these subjects, this will reveal information on the influence of skill-training on the activity of common corticospinal inputs. A difference in MU synchronization in skill-trained subjects compared to untrained subjects would suggest a neural adaptation of the corticospinal pathway to the constant performance of a skilled task.

1. 5. 3 Strength Training

As opposed to improvements in performance of a skilled task, strength-training is undertaken to obtain voluntary strength gains during the performance of a strength-related task. The increase in voluntary muscle force following a strength-training program results from two main factors: muscle hypertrophy and neural adaptations. Whereas muscle hypertrophy occurs in the later stages of training, strength increases are observed during the first weeks of training when there is no change in muscle size (Moritani & deVries, 1979;

Jones & Rutherford, 1987). These early strength gains are believed to be a result of neural adaptations, which can occur by increasing the intensity and extent of MU activation (including increasing the period during which full activation can be maintained during a continual maximal effort), and improving coordination among the synergists and antagonists (see Sale, 1988 for a review).

Considerable support for a neural contribution in strength-training comes from the interaction between different limbs, where training of one limb can promote an improvement in performance in the untrained contralateral limb, or there can be a reduction in maximal strength of one limb when the contralateral limb is also maximally activated (see Enoka, 1988 for a review). Recent evidence suggests that the maximal voluntary strength of a hand muscle can even be enhanced by training with *imagined* maximal contractions (Yue & Cole, 1992). Despite extensive evidence of these interesting phenomena, the mechanisms responsible for neural adaptations to strength-training are poorly understood. Over the years, major contributions to the understanding of the neural adaptations to strength-training have been obtained using simple recording techniques. The findings using surface EMG and single MUs will now be discussed below.

1.5.3.1 EMG studies

The most common method used to assess neural adaptations to strength-training is to record the surface EMG activity in prime movers during brief isometric contractions before and after training. The recorded EMG activity is rectified and filtered and is quantified as the integrated electromyogram (IEMG). IEMG has been shown to increase during the first 3-4 weeks after strength training involving weightlifting (Moritani & deVries, 1979; Häkkinen & Komi, 1986), isometric contractions (Komi *et al.* 1978), isokinetic eccentric contractions (Komi & Buskirk, 1972), and explosive jumping (Häkkinen *et al.* 1985). These findings are interpreted as indicating that strength-trained subjects can more fully activate muscles during MVCs (Sale, 1988), or possess a more rapid MU recruitment with higher discharge rates (McComas, 1994).

A further technique used to infer changes in MU activation is to measure the degree to which reflexes are modified by training. This method generally consists of quantifying the reflex responses to supramaximal peripheral nerve stimulation during rest and comparing it to the size of the response during MVCs. This is based on the assumption that the amplitude of the reflex during a MVC is correlated with the degree of MU activation, where a larger reflex is indicative of an increased ability to more fully activate MUs. Using this technique, it has been shown that reflex potentiation is greater in weightlifters than control subjects (Milner-Brown *et al.* 1975; Sale *et al.* 1983b). Furthermore, strength training has been shown to cause an increase in reflex potentiation (Milner-Brown *et al.* 1975; Sale *et al.* 1983a; Sale *et al.* 1983b), but the effect has not been observed in all muscle groups investigated (Sale *et al.* 1982; Sale *et al.* 1983b).

1.5.3.2 MU discharge properties

There is evidence to suggest that the discharge properties of MUs can be altered by training. After repeated fatiguing contractions, some subjects achieved higher MU firing rates and increased the duration of maximum MU discharge during MVCs (Grimby *et al.* 1981). Cracraft & Petajan (1977) have shown that the type of training can affect the firing pattern of TA MUs. They found that MUs fired less regularly following a program of high-intensity, short-duration exercise (strength-training), while more regular MU discharge was the result of a program of low-intensity long-duration exercise (endurance-training). Interestingly, it is the jaw-closing masseter muscle which has the highest MU discharge variability of all the commonly tested muscles (Nordstrom *et al.* 1990), and the jaw closing muscles are known to produce extremely large forces (Miles & Nordstrom, 1995).

Another MU discharge property that may be altered by strength-training is the independence of discharges in different MUs. This can be assessed during voluntary contractions by examining the degree of MU synchronization in a muscle which has been trained (see section 1.4). In the only previous study to examine the effect of strength training on MU synchronization, which used an indirect method of assessing MU synchrony from the surface EMG (see section 1.4.4.1 for details), it was reported that MU synchronization was

enhanced in individuals who regularly used their muscles to exert large, brief forces (Milner-Brown *et al.* 1975). It was also demonstrated in the same study that MU synchronization increased after a short period of intense muscular strength-training in FDI. Details on this issue can be obtained from section 1.4.4.1.

1. 5. 4 The mechanisms of neural reorganisation

There are two main mechanisms proposed for reorganisation of the nervous system. These are the growth of new connections, commonly termed collateral sprouting, and the alteration in effectiveness of previously existing connections (see Devor & Wall, 1981; Kaas, 1991).

Collateral sprouting, where denervated tissues act as a growth stimulus to form new synapses, is a process which has been shown to take a long period of time (Raisman & Field, 1973). Since neural adaptations to training appear to take place over several weeks, sprouting of central axons is unlikely to underly early improvements in performance. It has been suggested that the growth of axons and dendrites may not be of sufficient magnitude to be the major factor in neural reorganisation (Stelzner & Keating, 1977; Baisden *et al.* 1980; Rodin & Kruger, 1984), but may be more beneficial in developing brains (Kaas, 1991). Clear experimental evidence is needed to determine if sprouting of axons is a functionally effective mechanism in neural reorganisation following training.

In contrast, the mechanisms of altering the effectiveness of previously existing pathways appear to be widespread enough to account for most observed neural reorganisations, although most of these studies have been restricted to the reorganisation due to peripheral or CNS lesions. Alterations in the effectiveness of existing connections could occur by the potentiation of existing synapses or unmasking of previously ineffective ones. It is generally considered that there are a number of mechanisms which may increase the effectiveness of pre-existing synapses. Firstly, there is a possibility of the renewal of synaptic boutons, which is a feature of a reorganising cortex after lesions (Ganchrow & Bernstein, 1981), and there may be alterations in synapse shape, number, size and type (Markus & Petit, 1989). Secondly, the excitatory amino acid receptor (*N*-methyl-D-aspartate; NMDA) has been

implicated in cortical reorganisation. The NMDA receptor regulates the flow of calcium ions into neurons, which may be a factor in enhancing synaptic efficacy (Bear *et al.* 1987; Kleinschmidt *et al.* 1987). Finally, some structures have inputs that are normally subthreshold or unexpressed, but they may gain potency once the dominant inputs have been removed (Rhoades *et al.* 1987), or by deactivation of inhibitory connections (Wall, 1977).

Since many of these changes are quite rapid following lesions, over hours to days (Kaas, 1991), most investigators favour the interpretation that the short-term neural adaptation to amputation or other peripheral manipulations occur as a result of the potentiation of previously existing connections. This possibility has been demonstrated in animals following nerve section (Merzenich *et al.* 1983; Jenkins *et al.* 1990a). This also seems the most likely possibility to account for the less dramatic short-term changes which occur as a result of training. As direct corticospinal projections are necessary for fine control of the digits, it is likely that the improvement in performance of a skill requiring independent digit use would occur as a result of a modification in the effectiveness of the corticospinal pathway by either increasing the activity of corticospinal neurons, or increasing the effectiveness of their connexions with motoneurons. This suggests that the motor cortical projections may undergo changes according to different patterns of use. It may be that the learning of highly skilled tasks involving independent use of the digits (whether it be preferred use of the hand or learning to play a musical instrument) is accompanied by increased effectiveness of the corticospinal inputs targeting muscles involved in the task. Alternatively, automation of a task performed with a skilled hand may involve reduced activity in the direct corticospinal projections, and relegation of the task to less direct descending pathways. Under this scenario, performance of a simple task by a highly trained hand may require *less* activity in the corticospinal pathway. At present, there is little information to guide us on this question.

1.6 Physiological tremor

Physiological tremor is a low-amplitude, involuntary oscillation in force or position that can be demonstrated in nearly all normal subjects during voluntary activation of muscle. Physiological tremor is not present in the totally relaxed limb, but increases in parallel with the activation of muscles to maintain a fixed posture or to exert a force against an external object (Sutton & Sykes, 1967b). The predominant frequency of physiological tremor is between 6-12 Hz, but can vary depending on the age of the subject (Marsden *et al.* 1969a), the part of the body being examined (Marshall, 1970) and the technique used to record the tremor (Dietrichson *et al.* 1978; Marsden, 1978).

1.6.1 Physiological tremor production

A number of different mechanisms have the potential to contribute to tremor. These include mechanical properties of the extremity, or inputs from the CNS such as segmental reflex mechanisms, oscillatory driving of MUs by some CNS mechanism, or the interaction between firing patterns of MUs (discharge rate, variability, synchronization) that are transduced into mechanical events by the muscle. The degree to which each can influence physiological tremor is dependent on the particular experimental arrangement, such as the method used to record the tremor (force, velocity or acceleration), the site of recording, the muscles involved in the task (whether postural support against gravity is required) and the force of contraction required. During constant force isometric contractions requiring no postural support, the major factor responsible for the 6-12 Hz tremor is from the discharge characteristics of the underlying MUs. These are the conditions under which physiological tremor was examined in the present series of investigations (see Chapters 2 and 4).

1.6.2 Central nervous system factors affecting physiological tremor

In order to grade or adjust the degree of force exerted, the CNS either increases the firing rates of the already recruited motoneurons or recruits additional motoneurons (see section 1.1.2). The order of recruitment of these additional motoneurons occurs in a relatively fixed, reproducible manner, i.e. "the size principle" (Henneman, 1957; Henneman *et al.*

1965b). Not only are the larger motoneurons recruited after smaller ones, but the larger (i.e. last recruited) motoneurons are likely to be the ones discharging at sub-tetanic rates in any voluntary contraction, and they will contribute the largest fluctuations to the force profile. If, during a normal voluntary contraction the MUs discharge asynchronously, the fluctuations in force therefore arise from the partially fused contractions of MUs which have twitch profiles that produce the largest force (Marshall & Walsh, 1956; Allum *et al.* 1978). As the minimal firing rates of all MUs in a muscle are similar, and increases in force are accompanied by the recruitment of larger MUs, then the frequency of tremor is not likely to change much with increasing force, but the amplitude of tremor should increase in parallel. The observation that there is minimal change in tremor frequency with increasing contractile force while tremor amplitude increases monotonically has been supported by a number of investigators (Halliday & Redfearn, 1956; Sutton & Sykes, 1967b; Lippold, 1970; Joyce & Rack, 1974).

Both experimental (Allum *et al.* 1978) and modelling studies (Christakos, 1982) have shown that the 6-12 Hz component of tremor is strongly influenced by the unfused twitch profile of the recently recruited MUs. These studies have indicated that the spectral peak and the oscillations it represents are due to the activities of the relatively large units discharging near their recruitment rates. Given this concept of physiological tremor, differences in mean MU discharge rates, variability (Elek *et al.* 1991), synchronous discharge (Christakos, 1982) and common fluctuations of mean discharge rates (Elble & Randall, 1976) may all influence tremor.

Differences in mean MU discharge rates can affect tremor by altering the relative twitch fusion of the muscle fibres. At low motoneuron discharge rates, the muscle force fluctuates due to the partial relaxation of the muscle fibre before the next discharge (unfused tetanus). As the discharge frequency is increased, the force oscillations diminish in size until a critical frequency is reached when a smooth force output is achieved (fused tetanus). This critical frequency depends on the speed of contraction of the muscle fibres and can vary from 20 Hz for the soleus muscle up to 50 Hz for hand muscles (Marsden, 1978). The same is true for single MUs (Milner-Brown *et al.* 1973a); as the firing frequency is increased the MU

contributes less and less to the fluctuations in force. Therefore, given a repetitive firing frequency of a MU, the resultant oscillations in force will be large at low frequencies and small at higher frequencies. This effect can be even more pronounced given a greater MU discharge variability (Elek *et al.* 1991). The large range in MU discharge rate and variability in different individuals (Nordstrom *et al.* 1992) could be responsible for differences in physiological tremor commonly observed during isometric contractions in different individuals (Halliday & Redfearn, 1958; Elble & Randall, 1976).

The role of supraspinal inputs in the development of physiological tremor is unclear. It is apparent from a number of studies that the brain has the potential to influence physiological tremor in certain situations. The most convincing evidence that the CNS contributes to tremor is supported by the finding of Furness *et al.* (1977). This study examined the long lasting effects (up to four hours) of intense brief effort on the tremor of both intrinsic and extrinsic hand muscles. Through power spectral analysis, they found that finger tremor increased following a fatiguing contraction, but only if the muscle had been activated voluntarily, and not if the fatigue was induced by electrical stimulation of the muscle nerve (Furness *et al.* 1977). Tremor was also enhanced following unsuccessful voluntary attempts to move the finger with the arm paralysed by ischaemic nerve block (Furness *et al.* 1977).

MU synchronization, which is likely to provide information on the activity of corticospinal inputs, has the potential to be a significant factor influencing the amplitude of tremor exhibited within a muscle. Although theoretical modelling studies have shown that MU synchronization is not necessary for tremor, they predict that the amplitude of tremor would be enhanced by a tendency towards MU synchronization (Christakos, 1982). The effect of MU synchronization would be large particularly if the MUs which are firing just below their tonic firing frequency are synchronized. However, the extent to which the rather weak MU synchronization seen in most muscles influences the precision of force production remains unclear.

The idea that MU synchronization increases tremor amplitude has been assessed indirectly by Allum *et al.* (1978). In that study, the authors increased MU synchronization through

manipulation of the stimulation pattern of groups of ventral root filaments, which resulted in increased force fluctuations in a cat hind limb muscle. Using a more physiological approach in humans, only two previous studies have directly compared MU synchronization and tremor in the same muscle, with conflicting results. Dietz *et al.* (1976) found a correlation between MU synchronization and tremor amplitude in FDI and gastrocnemius/soleus, while Logigian *et al.* (1988) found no significant relationship between synchrony and physiological tremor using ECR MUs. However, in the light of more recent work, a number of methodological considerations have been emphasised in the collection, assessment and analysis of MU data for cross-correlation purposes. It is now known that there are large differences in the strength of synchrony in different MU pairs in a single muscle during the same task (Bremner *et al.* 1991a; Nordstrom *et al.* 1992) which indicates the necessity to sample from a large number of MU pairs to reliably assess the overall extent of synchrony within a muscle. Both Dietz *et al.* (1976) in the FDI (16 MU pairs in 6 subjects) and gastrocnemius/soleus (22 MU pairs in 6 subjects) and Logigian *et al.* (1988) in ECR (19 MU pairs in three subjects) sampled from a relatively small number of MU pairs. Considerable within-subject and between-subject variation also highlights the need to assess MU synchronization in many different subjects. It is also now known that indices which use the counts in a single peak bin as a measure of MU synchronization, such as that used by Dietz *et al.* (1976), are less reliable than indices based on the area of the peak which may extend for tens of milliseconds. Even with the index SI, which is the index based on peak area used by Logigian *et al.* (1988), the strength of MU synchronization observed in the cross-correlation histograms has been shown to be affected by the firing rates of the contributory MUs (Nordstrom *et al.* 1992). It is an aim of the present investigations to examine the relationship between the strength of MU synchronization and physiological tremor once all of the above conditions have been optimised. These include studying a larger population of subjects, with a more extensive sampling of MUs per muscle, and improving the estimation of synchrony by using longer periods of tonic discharge and new methods of quantifying synchrony from the cross-correlogram (Nordstrom *et al.* 1992).

The primary focus of the experiments described in Chapters 2 and 4 was to examine whether

MU discharge properties influence physiological tremor. A secondary interest in these experiments was related to the properties of MU discharge in individuals with different long-term patterns of muscle use. If the MU discharge properties (some of which indicate activity in the corticospinal pathway) are different in these groups of individuals, it would be important to know whether this would influence physiological tremor. If MU synchronization is altered by long-term muscle usage patterns (such as in Chapters 2 and 4), is that detrimental to the precision of force control (increased or decreased tremor)? This issue has not been addressed prior to the current investigations.

CHAPTER 2

INFLUENCE OF HANDEDNESS ON MOTOR UNIT DISCHARGE PROPERTIES AND FORCE TREMOR

2.1 Introduction

A recent study has shown that MU discharge properties in the FDI of the human hand vary considerably between different individuals (Nordstrom *et al.* 1992). In that study of seven subjects, there was a two-fold range in the mean coefficient of variation (CV) of interspike intervals in single MUs in different subjects, and a twenty-fold range in the mean strength of synchronization (a greater than chance probability that a pair of MUs discharge within a few milliseconds of each other) in MU pairs in the subjects. These aspects of MU discharge are important for motor control, as the variability and independence of MU discharge ultimately limit the precision of force production (Taylor, 1962; Elek *et al.* 1991; Christakos, 1982). In addition, evidence exists suggesting that MU synchronization reveals details of the distribution of branched inputs to motoneurons from common last-order neurons (see section 1.4.2). A narrow synchronous peak (within ± 8 ms of the firing time of the reference unit) is prominent in cross-correlograms of MU discharge in intrinsic hand muscles (Datta & Stephens, 1990; Bremner *et al.* 1991b; Nordstrom *et al.* 1992) and has been termed "short-term" synchronization. The narrow synchronous peak principally reflects shared, monosynaptic projections to motoneurons from CM cells via the lateral corticospinal tract (see section 1.4.3). It is possible that the large differences in the control properties of FDI MUs in different subjects observed by Nordstrom *et al.* (1992) are related to muscle usage patterns.

To address this question, it was necessary to compare the FDI MU discharge patterns in the

dominant and non-dominant hands of normal individuals. It is hypothesised that MU synchronization would be more prominent in the dominant hand, in keeping with the finding that there are more pyramidal tract fibres directed to the right than the left hand in about 75% of human brains (Nathan *et al.* 1990), and the principle that monosynaptic inputs to motoneurons from lateral corticospinal tract connections are necessary for fine control of the digits (Kuypers, 1981; Bortoff & Strick, 1993) and important for MU synchronization (Farmer *et al.* 1990; Datta *et al.* 1991). Sensorimotor representation of the dominant hand in monkeys occupies a larger area of the motor cortex than that of the non-dominant hand (Nudo *et al.* 1992). There is evidence that increased specialised use of a finger in Braille readers can change motor cortical representation of muscles in the reading finger (Pascual-Leone *et al.* 1993), and the threshold for excitation of an intrinsic hand muscle by TMS in humans is lower in the hemisphere controlling the preferred hand (Triggs *et al.* 1994). It has been reported that MU synchronization increased after a short period of intense muscular training in FDI (Milner-Brown *et al.* 1975), and a recent study has reported higher synchrony in wrist extensor MUs of the preferred arm (Schmied *et al.* 1994). The possibility exists that a lifetime of training from preferred use of a hand, or anatomical constraints in the projections of the corticospinal tract, may result in differences in MU discharge properties that reflect differences in CM projections in dominant and non-dominant hands.

The second aim of this study was to explore the relationship between hand preference and finger tremor. It is possible that control differences in the dominant and non-dominant hands might contribute to differences in finger tremor when tested during a force-matching task under visual control at low force levels. Marsden *et al.* (1969b) found no difference in finger tremor between hands, but in their study the subjects performed without feedback of their performance. In subjects provided with force feedback, Loscher & Gallasch (1993) have recently reported that force tremor is higher in the non-dominant hand of RH subjects during isometric power grip over a range of forces. It has been suggested that visual feedback modifies tremor (Sutton & Sykes, 1967a), although others could find no consistent effect (Stephens & Taylor, 1974). The idea that the CNS contributes to tremor is supported

by the finding that finger tremor increases following a fatiguing contraction, but only if the muscle has been activated voluntarily, and not if the fatigue is induced by electrical stimulation of the muscle nerve (Furness *et al.* 1977). Tremor is also enhanced following unsuccessful attempts to move the finger with the arm paralysed by ischaemic nerve block (Furness *et al.* 1977).

Finally, the importance of MU discharge properties (rate, variability, synchronization) for physiological force tremor is unknown. A number of potential mechanisms may contribute to tremor, including: the discharge patterns of MUs that are transduced into mechanical events by the muscle, mechanical properties of the extremity, segmental reflex mechanisms (which may reinforce mechanical oscillations), and oscillatory driving of MUs by some CNS mechanism (reviewed by Stein & Lee, 1981). It was anticipated that force fluctuations would be larger if MUs in a muscle discharged less regularly (cf. Elek *et al.* 1991) and with higher synchronization (Christakos, 1982). MU synchronization is commonly implicated in tremor (Lippold *et al.* 1957; Elble & Randall, 1976; Elble & Randall, 1978; Stiles, 1980) although it has only been directly measured and correlated with tremor in two studies, with conflicting results (Dietz *et al.* 1976; Logigian *et al.* 1988). It is not clear whether the 20-fold range in the mean strength of MU short-term synchronization in FDI in different subjects (Nordstrom *et al.* 1992) is related to subject differences in the magnitude of physiological finger tremor (Halliday & Redfearn, 1958; Elble & Randall, 1976). A further aim was to extend on the study of Dietz *et al.* (1976) in FDI by studying a larger population of subjects, with a more extensive sampling of MUs per muscle, and improving the estimation of synchrony by using longer periods of tonic discharge and new methods of quantifying synchrony from the cross-correlogram (Nordstrom *et al.* 1992).

2.2 Methods

Twelve healthy males (ages 21-47 years) volunteered to participate in the study and gave informed consent to the procedures. The experiments were approved by the Ethics

Committee for Human Experimentation at the University of Adelaide, and were conducted in accord with the recommendations of the Declaration of Helsinki for Human Experimentation. For each subject, the preferred hand for writing was designated the dominant hand. The degree of hand dominance was assessed by a 12-point questionnaire (Edinburgh inventory test; Oldfield, 1971), the details of which is shown in Appendix A. A laterality quotient (LQ) was calculated for each subject based on the answers to the questionnaire. Strong hand preference in a task (never use the opposite hand) was assigned two points, otherwise one point was given for each answer. LQ was given by the sum of the RH - LH preference points, as a proportion of the total points given.

2. 2. 1. Experimental apparatus

Subjects were seated with their right or left arm and hand secured in a manipulandum to ensure that a stereotyped position was maintained for each experiment (see Plate 2.1). The index finger abduction force signal (DC) was recorded on FM tape (Vetter model 400D, 22 kHz/ch). Force was bandpass filtered (1 - 50 Hz) and amplified (5-10x) prior to recording, to provide a high-gain signal suitable for evaluating tremor.

MU activity was recorded simultaneously with two separate fine-wire electrodes inserted percutaneously into the FDI. Each electrode consisted of two Teflon-insulated fine wires (45 μm core diameter) threaded through the lumen of a 25-gauge disposable needle. The distance between the two electrodes was generally 1-2 cm and were positioned in a direction perpendicular to the long axis of the muscle fibres. After insertion, the needle was removed leaving the fine wires in the muscle. Three wires were used with every needle insertion which avoided the necessity of inserting another electrode if one of the wires were deemed to be faulty. This also allowed three possible combinations of pairs of wires, which enabled the selection of the pair which gave the clearest discrimination of one or more MU action potentials. MU action potentials were amplified (1000x), filtered (bandwidth 2 Hz-10 kHz) and recorded on FM tape for off-line analysis.

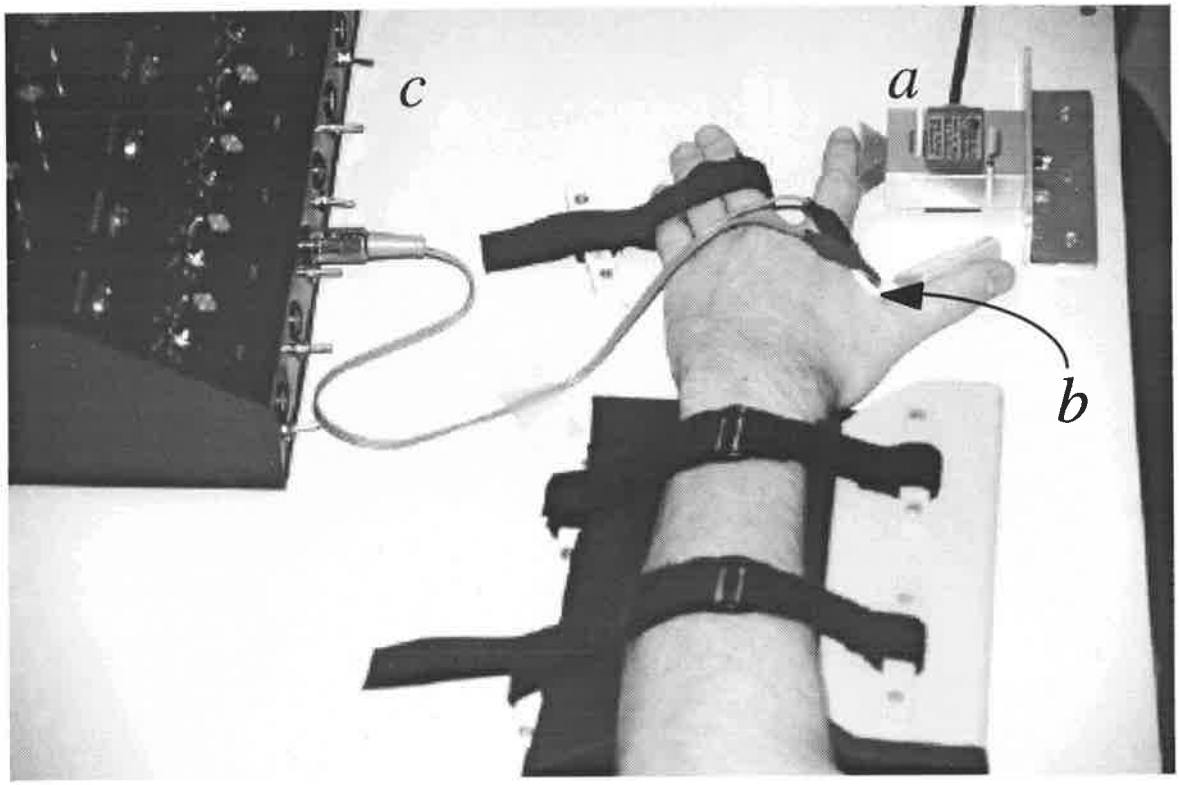

Plate 2.1 The manipulandum used for recording index finger abduction force and the electromyogram from the first dorsal interosseous muscle.
The arm and hand were secured by two restraints over the forearm, a support for the thumb and a strap over the second to fourth fingers. The hand was placed so that the distal interphalangeal joint of the index finger was aligned with a load cell that measured the force of abduction. The surface EMG of the FDI was recorded with electrodes overlying the muscle running parallel with the muscle fibres. Two or more intramuscular fine-wire electrodes were inserted into the belly of the muscle to record single motor unit activity (electrodes not shown). The manipulandum was designed to restrict the contribution of the index finger abduction force to the FDI, and minimise the contribution from other muscles.

The labelled components are: ***a***; force transducer,
b; surface EMG electrodes,
c; EMG amplifier.

The surface EMG of the left and right FDI was recorded with bipolar Ag-AgCl electrodes. The skin surface was prepared with alcohol, and conducting gel was applied to the recording surface of the electrodes. The surface electrodes were placed 2-3 cm apart near the centre of the muscle and aligned with the long axis of the muscle fibres. As opposed to conventional grounding techniques, an earth electrode was attached to the lower lip of the subject because of its ease of use (Türker *et al.* 1988). Surface EMG signals were amplified (1000x), filtered (bandwidth 2 Hz-10 kHz) and recorded on FM tape for off-line analysis. A transistor-transistor logic (TTL) pulse at 5-s intervals was also recorded on tape for the duration of the experimental run.

2.2.1.1. Protocol 1: MU Discharge Properties.

The MU recordings from left and right hands were made on separate days. Subjects performed a steady, low-force, isometric abduction of the index finger to activate MUs from within FDI. A single MU was chosen by the experimenters for the subject to control at a comfortable discharge rate (termed the feedback unit). The feedback MU was usually the MU with the largest waveform. With the use of an amplitude discriminator, subjects were given audio feedback of MU discharge, as well as visual feedback of mean discharge rate of the feedback unit on an oscilloscope screen. The subject's task was to control the mean firing rate of the feedback unit at a constant level for 3-5 min. The activity of additional MUs was monitored during the trial to ensure that no MU potentials were common to both pairs of electrodes, and to confirm that discriminable MU potentials were present in each channel for off-line cross-correlation. Subjects rested for at least 2 min following each trial, during which one or both electrodes were repositioned by pulling gently on the wires, or a new combination of wires were selected to sample from different MUs. Trials were then repeated with each new combination of active MUs. In this way a large number of MUs were sampled in a single experiment. During different trials, each new MU was assigned an individual identifier if it was considered to be a unique MU. In order to avoid cross-correlating the same MU pair, the MU waveforms from each electrode were consistently monitored during repositioning of the wires to ensure that different MUs were selected in

different trials. If a MU in a separate trial was deemed to have a similar waveform and discharge characteristics as the previous trial, it was assigned the same identifier. Due to the weak contraction levels performed, the same MU in a single electrode was usually monitored more than once during separate trials, but every attempt was made to establish a unique pair of MUs in each trial for cross-correlation. Using this method, it was unlikely, although not impossible, that the same MUs (with different identifiers) were cross-correlated more than once in a single experiment.

2.2.1.2. Protocol 2: Tremor during force matching.

Subjects attended the laboratory on two separate occasions to assess force tremor in FDI from both hands (two subjects were tested only once). The surface EMG of the left and right FDI was recorded with bipolar Ag-AgCl electrodes placed 2-3 cm apart. The subject's arm and hand were secured in the manipulandum and they were shown the output of the load cell on an oscilloscope screen. Following a period of familiarisation and practice, the subjects were required to produce a steady index finger abduction that matched as closely as possible, a target force level on the oscilloscope for 60-s. Target forces were 0.5 and 3.5 N, corresponding to approximately 1% and 7% of maximal force, respectively. Hands were tested in random order, with 1 min rest between trials, and the test sequence progressed from smallest to largest target force. The final test in each hand was maximal index finger abduction. The largest of three attempts was taken as the maximum force.

2.2.2. Analysis

2.2.2.1. MU discharge

All analyses were performed off-line from the taped records. Single MUs were discriminated using a computer-based template-matching algorithm (SPS 8701; *Signal Processing Systems*) which identified a particular MU on the basis of waveform shape. The signal from each intramuscular electrode pair was led to the SPS 8701 and analysed separately. To ensure that each MU from a particular trial was discriminated from the same starting point, the SPS 8701 was triggered to start from a TTL pulse which was recorded on

a separate channel of the tape recorder. When discriminating from a multiunit recording, the computer-based template matching system accepted the waveform of all action potentials which crossed an adjustable voltage threshold level. Each accepted waveform was matched to one of three templates which were selected from a preliminary, spike-by-spike analysis of the multiunit signal. An adjustable tolerance level assigned to the three templates accounted for small variations in waveform shape and background noise. If the action potential waveform did not match any of the selected templates to a given tolerance level, then it was rejected. Using this method, the activity of up to three MUs could be followed simultaneously. Great care was taken to confirm the identity of units discriminated during different trials by repeated examinations of the same segments of data and by adjusting the discrimination parameters. All unclassified spikes were examined and usually identified as superimpositions of two or more spikes. Interspike intervals (ISIs) of identified MUs were measured (± 250 μs resolution) using an in-built function of the SPS 8701 and stored on computer.

ISI records were scrutinised for every trial and each discriminated MU to assess discrimination accuracy (Nordstrom *et al.* 1992). An example is shown in Fig. 2.1.A. A characteristic sign of discrimination error (false-positive acceptance) was the presence of abnormally short ISIs (< 25 ms) which occur when action potentials of similar waveforms from different MUs are accepted as belonging to the identified MU. This is likely to occur if the adjustable tolerance level for the waveform is set too high. In Fig. 2.1.A, only two such intervals are seen. Most records used for analysis contained less than 1% of intervals < 25 ms. Records with more than 5% false positive acceptance errors were not used. False-negative intervals are also seen in Fig. 2.1.A as a banding of intervals at multiples of the mean ISI. These missed spikes can occur in multiunit recordings when MU action potentials are not recognised due to superimposition of the waveform with other waveforms from different MUs discharging at around about the same time. If the recorded MUs have a tendency for synchronous discharge, the effect of non-recognition due to superimpositions would be to slightly reduce the central peak in the cross-correlogram. As the strength of MU short-term synchrony in normal human muscles is extremely weak, the effect of missed

spikes due to superimpositions would be insignificant unless a large number of MU potentials are present in each electrode channel (see Nordstrom, 1989). Therefore, these missed spikes are not serious for the cross-correlogram, as it simply means less counts are available for the analysis.

ISI histograms were constructed from the discharge times of each MU (Fig. 2.1.B). Abnormally short and long ISIs that were clearly the result of discrimination error were excluded from statistical analysis (i.e. only the intervals between the dashed lines in Fig. 2.1.B were included). The cut-off limits were determined from visual inspection of the interval histogram to include only those intervals in the main distribution (around 100 ms in Fig. 2.1.B). The mean, standard deviation and CV (SD/mean x 100) of the main distribution of ISIs were determined using a commercially available statistical package (Statview II, Abacus Concepts). The removal of ISIs shorter than 25 ms would produce a slight tendency for a longer mean ISI, as any interval shortened by a spurious spike will be one of a pair, and the remaining interval (which would be slightly longer than the mean) would usually be accepted in the calculation of the ISI characteristics. However, the incidence of false-positive acceptances were extremely low (< 5%) in all recorded MUs, which would only produce a negligible effect on the mean ISI when considering the large number of accepted discharges for each MU.

2.2.2.2 Cross-correlation histograms

Cross-correlation analysis (Sears & Stagg, 1976; Datta & Stephens, 1990; Nordstrom *et al.* 1992) was used to determine the degree of MU synchronization, which is a measure of the time of firing of one MU in the muscle with respect to the firing of a second, reference unit. If there is no synchronous activity between MU pairs used for cross-correlation, the cross-correlogram will be flat (Moore *et al.* 1966). If a tendency towards synchronization exists, there will be a narrow synchronous peak in the cross-correlogram around the time of firing of the reference MU (see Fig. 2.2).

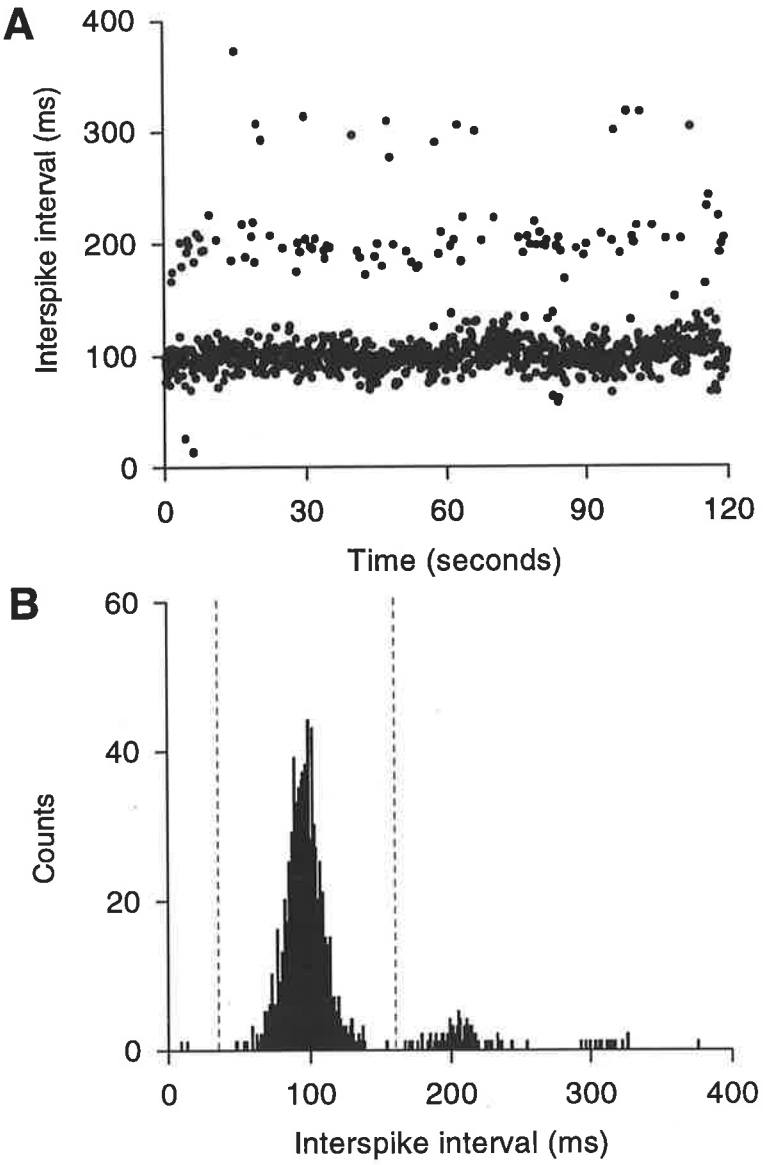

Figure 2.1 Verification of discrimination accuracy and calculation of discharge rate and variability.

A, ISIs of a MU discriminated from a multiunit record. ISIs shorter than 25 ms are indicative of false-positive acceptances. Only two such intervals are seen in the record, indicating a highly reliable discrimination. The banding of intervals at multiples greater than the main distribution are indicative of false-negative acceptances arising from superimpositions of other waveforms. ***B***, interval histogram of the record shown in A. The dashed vertical lines represent the cut-off limits of the ISI distribution selected by visual inspection to exclude intervals resulting from discrimination error. The intervals between the dashed vertical lines were used for the calculation of the mean ISI and the CV. For this MU, the mean ISI was 98.7 ms and the mean CV was 11.8%.

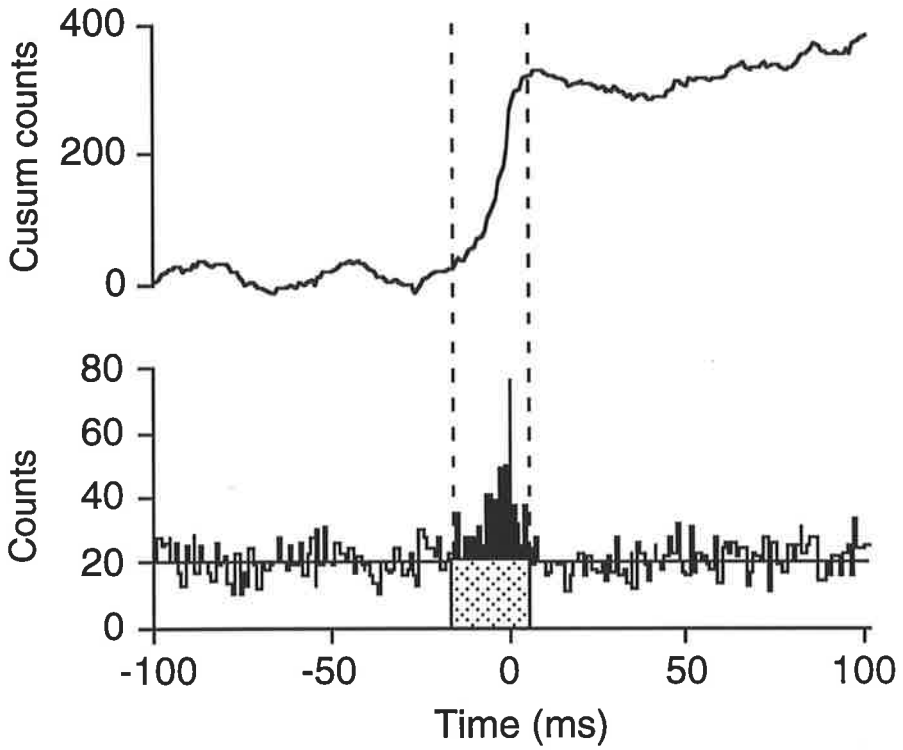

Figure 2.2 Quantification of the strength of motor unit synchronization from the cross-correlogram.

The lower trace shows the cross-correlogram of MU discharge from a pair of MUs in FDI muscle. The upper trace shows the corresponding CUSUM. The position and duration of the synchronous peak was judged visually from the CUSUM (dashed vertical lines). In this example, the width of the peak was 21 ms centred at t = -6 ms. The mean bin count in the region of the histogram outside of the peak was 20.9 counts (solid horizontal line). This value distinguished between those counts expected due to chance (dotted area) from those counts in excess of chance within the peak region (dark area). The synchronization index CIS was calculated by dividing the number of counts in excess of chance in the peak region (284.6 extra counts) by the duration of the trial (272.5 s). The synchronization index CIS for this MU pair was 1.01 extra counts per second.

ISI files created with the SPS 8701 were used to produce cross-correlograms of the discharge times of discriminated MUs. MUs detected with separate electrodes were paired for cross-correlation. All cross-correlograms had 1-ms bin widths and spanned a period 100 ms before and after the discharge of the reference unit (201 bins). Cross-correlation analysis was restricted to periods in which both units of the pair were tonically active. All cross-correlograms were plotted and examined for any irregularities, such as the cross-correlation of MUs common to both electrodes which results in a single bin containing most of the MU discharges. If this existed, other MUs from the same experimental trial were discarded from the analysis. Histograms with a mean bincount < 4 were not analysed further.

The cumulative sum procedure (CUSUM; Ellaway, 1978) was used to identify synchronous peaks in the cross-correlogram. The CUSUM is derived by subtracting the difference between the mean bin count of bins outside of the peak region in the cross-correlogram (taken as -100 to -30 ms from the time of discharge of the reference MU) from the number of counts in each bin. The differences are then consecutively added or subtracted to form a new series of points (upper trace, Fig. 2.2.). Any increase or decrease in the CUSUM level reveals small changes in the probability of discharge between the two MUs in the cross-correlogram. The position and duration of the cross-correlogram peak was judged visually from the CUSUM based on the points of major inflection around time 0 (dashed vertical lines, Fig. 2.2.). As the peak width is particularly difficult to assess during weak synchronization, reliability was maintained between cross-correlograms as the peak width was assessed by the same observer on all occasions. The significance of peaks in the cross-correlogram was assessed using a computer program based on the method described by Wiegner & Wierzbicka (1987). This required the calculation of a synchronization index (SI) for each cross-correlogram. The SI was calculated by dividing the number of extra counts within the peak by the total number of counts in the histogram. The SI for each histogram was compared with the critical value required for different levels of statistical significance. If no significant peak was identified from the cross-correlogram using this test, then a standard peak width of 11 ms, centred at time 0, was used for quantification of the strength of synchrony in that MU pair.

The magnitude of a synchronous peak in the cross-correlogram was quantified as the *frequency* of synchronous action potentials in the MU pair in excess of those expected due to chance. This is calculated by dividing the number of counts in the peak region in excess of chance (dark area, Fig. 2.2.) by the duration of the trial when both MUs were tonically active. This measure has been termed the synchronization index CIS, as it has been argued that it is directly related to the *C*ommon *I*nput *S*trength in the pair of MUs (i.e. the number and discharge frequency of shared branched-axon excitatory synaptic inputs, and their amplitude; Nordstrom *et al.*, 1992). An important advantage of the index CIS over other synchronization indices is that it is independent of the discharge rate of the MUs contributing to the cross-correlogram (Nordstrom *et al.* 1992). The finding that differences in firing rate does not influence the synchrony index CIS has been confirmed by other investigators (Schmied *et al.* 1993), and the index has since been accepted as a valid measure of the strength of MU synchronization in human muscles (Schmied *et al.* 1994; Mills & Schubert, 1995).

2.2.2.3 Force tremor

The high-gain force records from the force-matching trials were digitised (1 kHz sampling rate) with a Macintosh computer using the graphical programming language Labview (National Instruments, Austin, TX, USA). Four 5-s epochs from the beginning of each trial were digitally filtered (Fifth order Butterworth, bandwidth 4-30 Hz). This filter setting was chosen to minimise the low-frequency force fluctuations due to voluntary corrective efforts, so as to concentrate on those within the physiological tremor range (i.e. 6-12 Hz). The root mean square (RMS) errors of the filtered force records from each epoch were calculated, and the four values averaged to give an RMS error representative of the force-matching trial. The RMS error values from trials performed on separate days were averaged to provide the final RMS error in each force-matching trial for each subject. The power spectral density function of the high-gain force signal was calculated using a fast Fourier transform (FFT). Data from the same 5-s epochs used for the RMS error calculations were divided into blocks of 2048 samples (block duration approximately 2 s) prior to processing by the FFT, yielding a

frequency resolution in the power spectrum of approximately 0.5 Hz. Spectra from different epochs were averaged in the frequency domain to provide the final power density spectrum representative of each force-matching task for each subject. The peak tremor frequency and the power at the peak frequency were quantified from these force spectra. The peak tremor frequency was regarded as the frequency at which the most power was observed in the FFT.

2. 2. 3 Statistical Analysis

Data are presented as mean ± S.E. (n). Subjects were grouped by handedness (LH, RH) and hand (dominant, non-dominant). A two-way analysis of variance (ANOVA) was employed for comparisons of MU synchronization (CIS), mean ISI and CV between groups. The treatment of the force data involved the same groups, examined for tremor RMS amplitude, power at the peak tremor frequency and tremor peak frequency. Significant effects were analysed further with one-way ANOVA and Scheffe's F-test. Linear regression was used to assess the relationships between MU synchronization and discharge pattern, and MU synchronization and force tremor. For all analyses, significance was reported for $P < 0.05$.

2.3 Results

2. 3. 1 Discharge properties of individual MUs

Discharge properties of individual MUs, as assessed from the mean ISI and the CV of the mean ISI, were similar in both hands of left and right handers (Table 2.1). Mean ISI (± S.E.) for left handers was 100.7 ± 2.0 ms (n = 72) in the dominant hand and 102.2 ± 1.6 ms (n = 88) in the non-dominant hand. Mean ISI for right handers was 96.3 ± 2.3 ms (n = 89) in the dominant hand and 98.9 ± 2.1 ms (n = 94) in the non-dominant hand. Mean CV in left handers was 17.6 ± 0.5% (72) in the dominant hand *vs.* 16.1 ± 0.3% (88) in the non-dominant hand. Mean CV in right handers was 17.5 ± 0.5% (90) in the dominant hand *vs.* 17.6 ± 0.4% (96) in the non-dominant hand.

Table 2.1. Summary of two-way ANOVA comparisons for handedness and hand used for the task.

Dependent variable	*Effect*		
	HANDEDNESS	***HAND***	***Interaction***
Mean ISI	F[1,339] = 3.4 n.s.	F[1,339] = 1.0 n.s.	F[1,339] = 0.1 n.s.
Mean CV	F[1,339] = 2.6 n.s.	F[1,339] = 3.2 n.s.	F[1,339] = 3.6 n.s.
Mean CIS	F[1,356] = 5.8 P < 0.02	F[1,356] = 3.5 n.s.	F[1,356] = 9.0 P < 0.01
Synchrony Peak Width	F[1,262] = 30.5 P < 0.001	F[1,262] = 5.7 P < 0.02	F[1,262] = 10.9 P < 0.02
Tremor RMS (0. 5 N contraction)	F[1,20] = 5.6 P < 0.05	F[1,20] = 1.3 n.s.	F[1,20] = 0.8 n.s.
Tremor RMS (3. 5 N contraction)	F[1,20] = 2.2 n.s.	F[1,20] = 0.3 n.s.	F[1,20] = 0.0 n.s.
Power at peak tremor frequency. (0. 5 N contraction)	F[1,20] = 11.6 P < 0.01	F[1,20] = 9.6 P < 0.01	F[1,20] = 5.7 P < 0.05
Power at peak tremor frequency. (3. 5 N contraction)	F[1,20] = 2.9 n.s.	F[1,20] = 2.3 n.s.	F[1,20] = 0.8 n.s.
Peak tremor frequency (0. 5 N contraction)	F[1,20] = 0.1 n.s.	F[1,20] = 0.3 n.s.	F[1,20] = 4.1 n.s.
Peak tremor frequency (3. 5 N contraction)	F[1,20] = 0.02 n.s.	F[1,20] = 0.02 n.s.	F[1,20] = 0.0 n.s.

2. 3. 2 Incidence of significant synchronization peaks

The incidence of MU pairs with significant peaks in the cross-correlogram was not uniform in each hand of the LH and RH subjects (Table 2.2). Synchronization was much less

common between MUs from the dominant hand of right handers (51% of pairs), whereas the non-dominant hand of right handers and each hand of left handers had a similar incidence of synchrony, with about 80% of pairs having significant synchronization. These distributions were significantly different (chi-square = 9.2; $P < 0.01$).

Table 2.2. Incidence of significant synchronization of FDI MU pairs in right- and left-handed subjects.

	Incidence of significant synchronization		
	Dominant hand	*Non-dominant hand*	*Both hands*
Right handers	45/88 (51.1%)	90/111 (81.1%)	135/199 (67.8%)
Left handers	49/61 (80.3%)	82/100 (82.0%)	131/161 (81.4%)
All subjects	94/149 (63.1%)	172/211 (81.5%)	266/360 (73.9%)

2. 3. 3 Strength of synchronization peaks

Representative examples of cross-correlograms from the dominant and non-dominant hands of one RH and one LH subject are shown in Fig. 2.3. In each case, a significant synchronization peak is evident in the cross-correlogram. In this example, the strength of MU synchronization measured by the synchrony index CIS was lower in the dominant hand of the RH subject, and was between 55 and 65% strength of the non-dominant hand in the same subject, and both hands of the LH subject.

The mean strength of MU synchronization as assessed by the index CIS differed significantly between groups (Table 2.1). The mean CIS values of the groups, and significant post-hoc comparisons are summarised in Table 2.3. The main difference in the strength of MU synchronization in LH and RH subjects was that the dominant hand of right handers had much weaker synchrony (0.23 ± 0.03 s^{-1}) than the non-dominant hand of right handers (0.39 ± 0.03 s^{-1}) and dominant (0.41 ± 0.03 s^{-1}) and non-dominant (0.37 ± 0.03 s^{-1}) hands of left handers. For left handers, there were no significant differences in the strength of synchronization in the dominant and non-dominant hands.

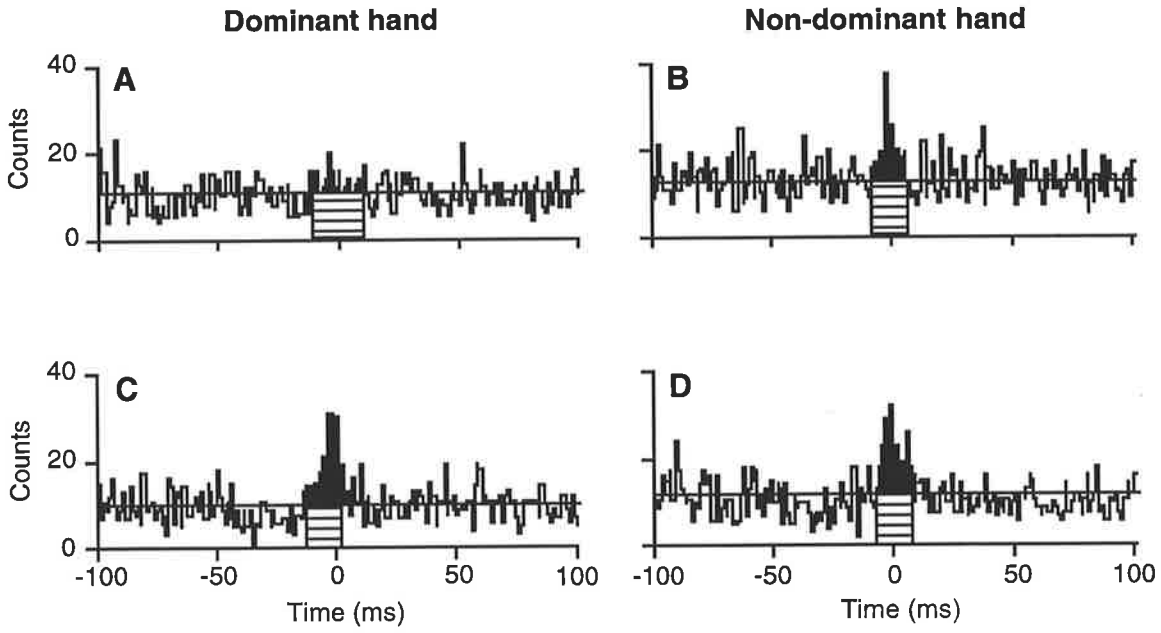

Figure 2.3 Representative examples of motor unit synchronization from the dominant and non-dominant hands of right-handed and left-handed subjects. ***A, B,*** RH subject. Each graph shows a typical cross-correlogram of the discharge times of two FDI MUs from the dominant (A) and non-dominant (B) hand of one subject. The solid horizontal line represents the mean bin count of the cross-correlogram from bins outside of the peak region. This distinguished between the counts expected due to chance (horizontally hatched area) from the extra synchronous discharges within the peak region (black area). ***C, D,*** LH subject, data arranged as in A, B. For the MU pairs shown, the strength of MU synchronization in the dominant hand of the RH subject (CIS = 0.37 s^{-1}) was between 55-65% strength of the non-dominant hand in the same subject (CIS = 0.59 s^{-1}) and the dominant (CIS = 0.60 s^{-1}) and non-dominant (CIS = 0.66 s^{-1}) hand of the LH subject. The width of the synchronous peak was also wider in the dominant hand of the RH subject (23 ms) compared to the non-dominant hand of the same subject (11 ms) and both hands of the LH subject (dominant *vs.* non-dominant, 15 ms *vs.* 13 ms).

Table 2.3. Strength of synchronization of FDI MU pairs in right- and left-handed subjects.

	Synchronization index (CIS)		
	Dominant hand	*Non-dominant hand*	*Both hands*
Right handers	0.23 ± 0.03 s^{-1}**§§ (88)	0.39 ± 0.03 s^{-1} (111)	0.32 ± 0.02 s^{-1} (199)
Left handers	0.41 ± 0.03 s^{-1} (61)	0.37 ± 0.03 s^{-1} (100)	0.38 ± 0.02 s^{-1}§ (161)
All subjects	0.30 ± 0.02 s^{-1} (149)	0.38 ± 0.02 s^{-1}* (211)	0.35 ± .02 s^{-1} (360)

Values are mean ± S.E. (n). * significant difference ($P < 0.05$) dominant *vs.* non-dominant hand. ** significant difference ($P < 0.001$) dominant *vs.* non-dominant hand. § significant difference ($P < 0.05$) for left- *vs.* right-handers. §§ significant difference ($P < 0.001$) for left- *vs.* right-handers.

The data from individual subjects supported the conclusion that MU synchronization was weaker in the dominant hand of right handers (Fig. 2.4). A two-way ANOVA (hand, subject) revealed significant effects on mean CIS for hand ($F[1, 336] = 4.7$, $P < 0.05$), subject ($F[11, 336] = 9.7$, $P < 0.001$) and the interaction ($F[11, 336] = 4.2$, $P < 0.001$). In five of six RH subjects synchrony was lower in the dominant hand, and differences were significant in four individuals (Fig. 2.4A). In LH subjects, there were no significant differences in synchronization strength between hands for any individuals (Fig. 2.4B). The corresponding LQ values for each of these subjects is provided in Table 2.4.

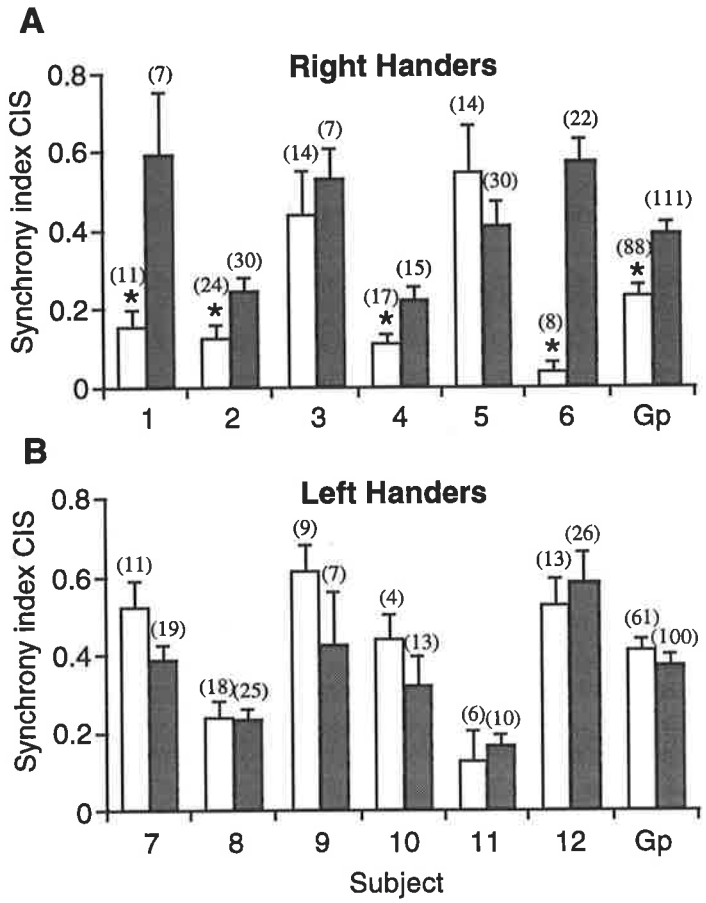

Figure 2.4 Mean strength of motor unit synchronization in each hand of right- and left-handed subjects.

A, mean values for synchronization index CIS for 6 RH subjects, dominant hand open bars, non-dominant hand shaded bars. Gp represents mean strength of MU synchronization in each hand averaged over the group. * significant differences (Scheffe's F test; $P < 0.05$) between hands in each subject. Numbers in brackets represent the number of MU pairs recorded in each hand for each subject. ***B***, mean CIS values for 6 LH subjects, arranged as in A. MU synchronization was significantly lower in the dominant hand in 4 of 6 RH subjects, but there were no significant differences between hands for LH subjects.

Table 2.4. Laterality quotient values in right- and left-handed subjects.

Right handers	***Laterality quotient***
Subject 1	0.71
Subject 2	0.50
Subject 3	0.83
Subject 4	1.00
Subject 5	0.81
Subject 6	0.88
Mean	0.79
Left handers	***Laterality quotient***
Subject 7	-0.75
Subject 8	0.17
Subject 9	-0.22
Subject 10	-0.71
Subject 11	-0.83
Subject 12	-0.75
Mean	-0.52

2. 3. 4 Width of significant synchronization peaks

There were significant differences in the width of significant synchronization peaks in the groups (Table 2.1). For right handers, mean width of significant peaks was 19.5 ± 1.2 ms (n = 45) in the dominant hand. This was significantly different (Scheffe's F test; $P < 0.01$) from the mean peak width in the non-dominant hand of RH subjects (15.5 ± 0.6 ms (90)), and the dominant (13.3 ± 0.7 ms (49)) and non-dominant (14.0 ± 0.5 ms (82)) hand of left handers.

2. 3. 5 Relationships between synchronization strength and discharge properties of MUs

The synchronization index CIS is not sensitive to the discharge rate of the MUs contributing to the cross-correlogram (Nordstrom *et al.* 1992), unlike other common synchronization indices. The geometric mean ISI was calculated for each unit pair used for cross-correlation (geometric mean ISI = √(mean ISI unit A x mean ISI unit B)). There was no significant

correlation between CIS and geometric mean ISI for the pooled data (Fig. 2.5A, $r^2 = 0.007$, n = 360). In any event, the discharge rates of MUs used for the cross-correlograms were similar for all group comparisons. For left handers, mean ISI of pairs used for cross-correlation was 100.0 ± 1.7 ms (n = 61) in the dominant hand and 102.0 ± 1.2 ms (n = 100) in the non-dominant hand. For right handers, mean ISI of cross-correlated pairs was 97.6 ± 2.2 ms (n = 88) in the dominant hand and 97.4 ± 1.4 ms (n = 111) in the non-dominant hand. There was no significant correlation between CIS and the difference in discharge rate of the MUs contributing to the cross-correlogram ($r^2 = 0.064$, n = 360).

For the data from all subjects in the present study, there was no significant correlation between CIS and the geometric mean CV of the units contributing to the cross-correlogram (Fig. 2.5B, $r^2 = 0.002$, n = 360). Similar non-significant correlations between these two variables were found in LH ($r^2 = 0.035$, n = 199) and RH ($r^2 = 0.023$, n = 135) subjects.

For the data from all subjects in the present study, there was no significant correlation between CIS and the geometric mean CV of the units contributing to the cross-correlogram (Fig. 2.5B, $r^2 = 0.002$, n = 360). Similar non-significant correlations between these two variables were found in LH ($r^2 = 0.035$, n = 199) and RH ($r^2 = 0.023$, n = 135) subjects.

2. 3. 6 Handedness and tremor

Examples of force tremor and tremor frequency power spectra for the dominant and non-dominant hands of a RH subject are shown in Fig. 2.6. These records were obtained during an isometric abduction of the index finger with a 0.5 N target force. In this example, the RMS tremor amplitude was slightly higher in the non-dominant hand (6.7 mN *vs.* 6.3 mN). The peak frequency in the power spectrum was similar for each hand, but the power at the peak frequency was much higher in the non-dominant hand (8.2 mN^2 vs 3.6 mN^2). This was an invariant finding in RH subjects (12/12 comparisons at the two target force levels), but not LH subjects (9/12).

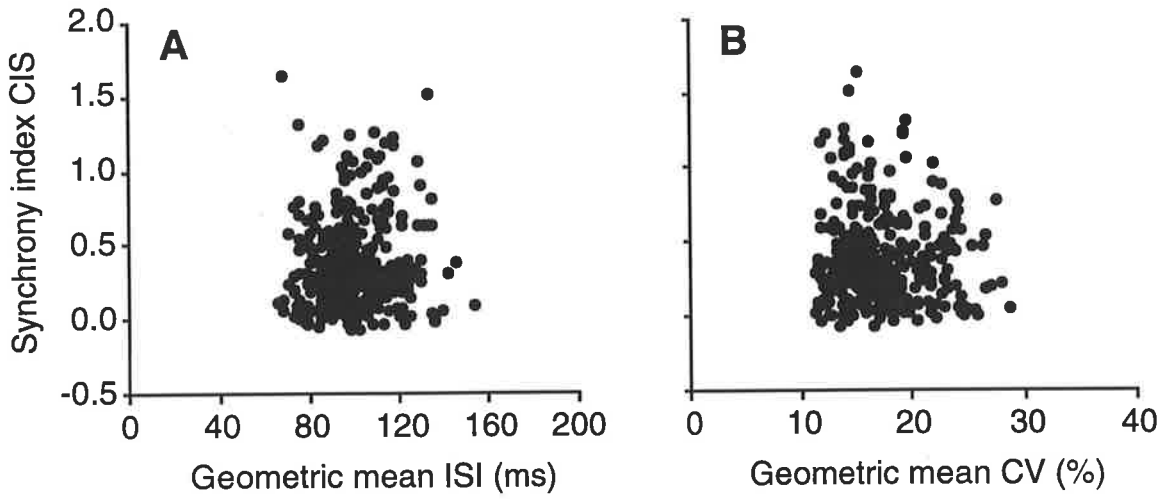

Figure 2.5 Relationships between motor unit discharge properties and motor unit synchronization.

A, Relationship between the geometric mean ISI of the 360 MU pairs contributing to the cross-correlogram and the synchrony index CIS. ***B***, Relationship between the geometric mean CV of the 360 MU pairs contributing to the cross-correlogram and the synchrony index CIS. No significant relationship was found between the synchrony index CIS and the geometric mean ISI ($r^2 = 0.007$) or the geometric mean CV ($r^2 = 0.002$).

The tremor data from all subjects are summarised in Fig. 2.7 for target forces of 0.5 N (Fig. 2.7A, C, E) and 3.5 N (Fig. 2.7B, D, F). There were no significant effects in the two-way ANOVA for any tremor variable measured during the 3.5 N target contraction (Table 2.1; Fig. 2.7B, D, F). Tremor RMS amplitude (Fig. 2.7A) was significantly different (Table 2.1) in LH (10.1 ± 1.6 mN) and RH (15.9 ± 1.8 mN) subjects at the 0.5 N target force. With the 0.5 N target force, power at the tremor peak frequency (Fig. 2.7C) was significantly higher (Scheffe's F test; $P < 0.01$) in the non-dominant hand of RH subjects than the dominant hand of RH subjects and both hands of LH subjects (see also Table 2.1). Tremor peak frequency was not influenced by hand preference or the hand used to perform the task for either the 0.5 N (Fig. 2.7E) or 3.5 N target forces (Fig. 2.7F).

Tremor amplitude was larger in the stronger contraction (Fig. 2.7A-B, C-D). Mean tremor RMS amplitude was 13.0 ± 1.3 mN ($n = 24$) at 0.5 N and 30.5 ± 2.7 mN ($n = 24$) at 3.5 N (Paired t-test, $P < 0.01$). Peak power was 6.1 ± 1.2 mN^2 ($n = 24$) at 0.5 N and 31.2 ± 5.7 mN^2 ($n = 24$) at 3.5 N ($P < 0.01$). In contrast, the peak frequency in the force spectrum was not influenced by contraction level (Fig. 2.7E-F). Mean tremor peak frequency was 6.2 ± 0.3 Hz ($n = 24$) at 0.5 N and 6.7 ± 0.3 Hz ($n = 24$) at 3.5 N ($P > 0.05$).

Tremor amplitude in the two hands was related. There was a significant positive correlation between the RMS tremor amplitude in the dominant and non-dominant hands of all subjects for the 0.5 N ($r^2 = 0.40$, $n = 12$, $P < 0.05$) and 3.5 N contractions ($r^2 = 0.76$, $n = 12$, $P < 0.01$). The same was true for the correlation between the power at the peak frequency of the force spectrum in the dominant and non-dominant hands at each force level (0.5 N, $n = 12$, $r^2 = 0.43$, $P < 0.05$; 3.5 N, $r^2 = 0.49$, $n = 12$, $P < 0.02$).

2. 3. 7 MU discharge properties and tremor

The relationships between MU discharge properties (rate, variability, synchronization) and force tremor during isometric abduction of the index finger were examined using linear regression analysis. Tremor was quantified at force levels of 0.5 N and 3.5 N, as this encompassed the range of forces comparable to conditions under which MU discharge was

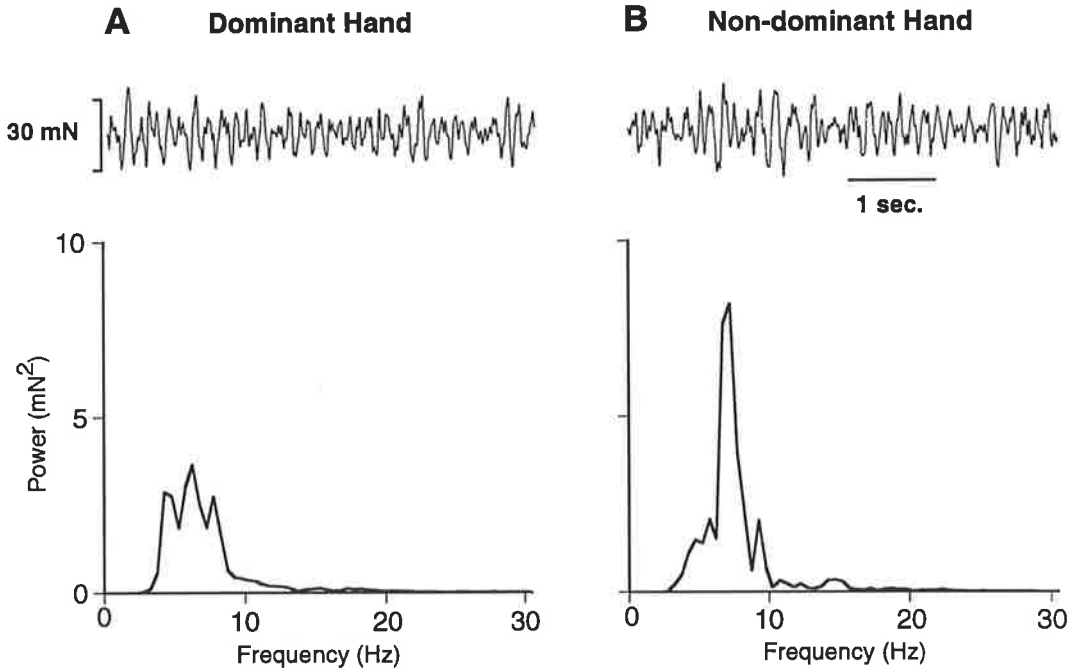

Figure 2.6 Representative examples of tremor in dominant and non-dominant hands of a right-handed subject.

A, Dominant hand. Upper trace shows a 5-s epoch of force fluctuations during a 20-s isometric abduction of the index finger with a 0.5 N target force. Force tremor RMS was 6.3 mN for this epoch. Lower trace shows the averaged frequency power spectrum for the 20 s trial. Tremor peak frequency was 5.9 Hz. ***B***, Non-dominant hand. Index finger isometric abduction with a 0.5 N target force, data arranged as in A. Force tremor RMS was 6.7 mN and tremor peak frequency was 6.8 Hz, comparable to values in the dominant hand. The power at the peak frequency in the force spectrum was much higher in the non-dominant hand (8.2 mN^2 *vs* 3.6 mN^2).

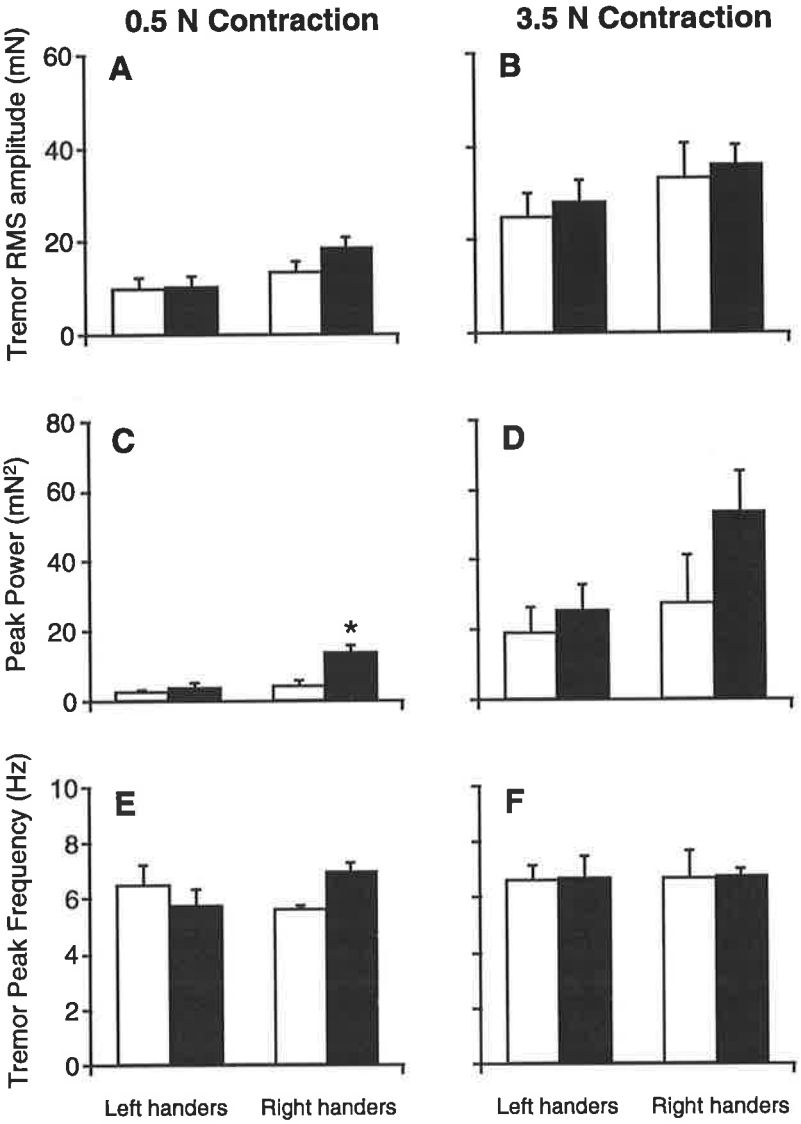

Figure 2.7 Summary of tremor amplitude and peak frequency for dominant and non-dominant hands of left- and right-handed subjects at two target force levels.

Open bars, dominant hand; filled bars, non-dominant hand. ***A***, mean (± S.E.) tremor RMS amplitude during isometric index finger abduction with the 0.5 N target force. ***B***, mean tremor RMS amplitude during isometric index finger abduction, 3.5 N target force. ***C***, Power at the peak frequency in the force spectrum, 0.5 N target force. ***D***, Power at the peak frequency in the force spectrum, 3.5 N target. ***E***, mean tremor peak frequency with the 0.5 N target. ***F***, mean tremor peak frequency with the 3.5 N target. * significant difference (Scheffe's F test; $P < 0.01$) non-dominant hand of right-handed subjects *vs.* dominant hand of RH subjects and both hands of LH subjects.

recorded. Abduction force was between 0.5 and 1 N in most MU experiments, and never exceeded 4 N.

There were no significant correlations between MU mean ISI in a muscle and tremor RMS amplitude or peak power in the force frequency spectrum. The correlations between MU discharge variability (mean CV of ISIs) and tremor were weak, and mostly non-significant. For pooled data from all subjects, there was no significant correlation between the mean MU CV and tremor RMS amplitude with either the 0.5 N (r^2 = 0.04) or 3.5 N (r^2 = 0.11) contraction (Fig. 2.8A, B). For the RH subjects alone there was a significant correlation (r^2 = 0.39; $P < 0.05$) between CV and tremor RMS amplitude for the 3.5 N contraction (Fig. 2.8B), but all other subgroups yielded non-significant correlations. For all subjects, mean CV was significantly correlated with the peak power in the force spectra for the 3.5 N contraction (Fig. 2.8D; $r^2 = 0.18$; $P < 0.05$), but not the 0.5 N contraction (Fig. 2.8C). For RH subjects alone there was a significant correlation between CV and peak power in the force spectrum for the 3.5 N contraction (Fig. 2.8D; $r^2 = 0.50$; $P < 0.05$); all other subgroups yielded non-significant correlations between these variables.

The overall strength of MU synchronization in a muscle was also a poor predictor of tremor. There were no significant correlations between mean synchronization strength (CIS) and RMS force tremor with either target force (Fig. 2.9A,B). For pooled data from both hands and all subjects, the relationship between mean synchronization strength (CIS) and peak power in the force spectra were weak for the 0.5 N (Fig. 2.9A, $r^2 = 0.12$, $P > 0.05$) and 3.5 N (Fig. 2.9B; $r^2 = 0.001$, $P > 0.05$) contractions. The only significant correlation between these variables was in RH subjects with both hands included, but only at the 0.5 N target force (fitted line in Fig. 2.9C; $r^2 = 0.35$, $P < 0.05$).

2.4 Discussion

The three main findings of this study were that 1) MU short-term synchronization in the FDI was weaker and broader in the dominant hand of RH subjects, 2) force tremor (RMS) was not consistently different in non-dominant and dominant hands, although the force spectrum

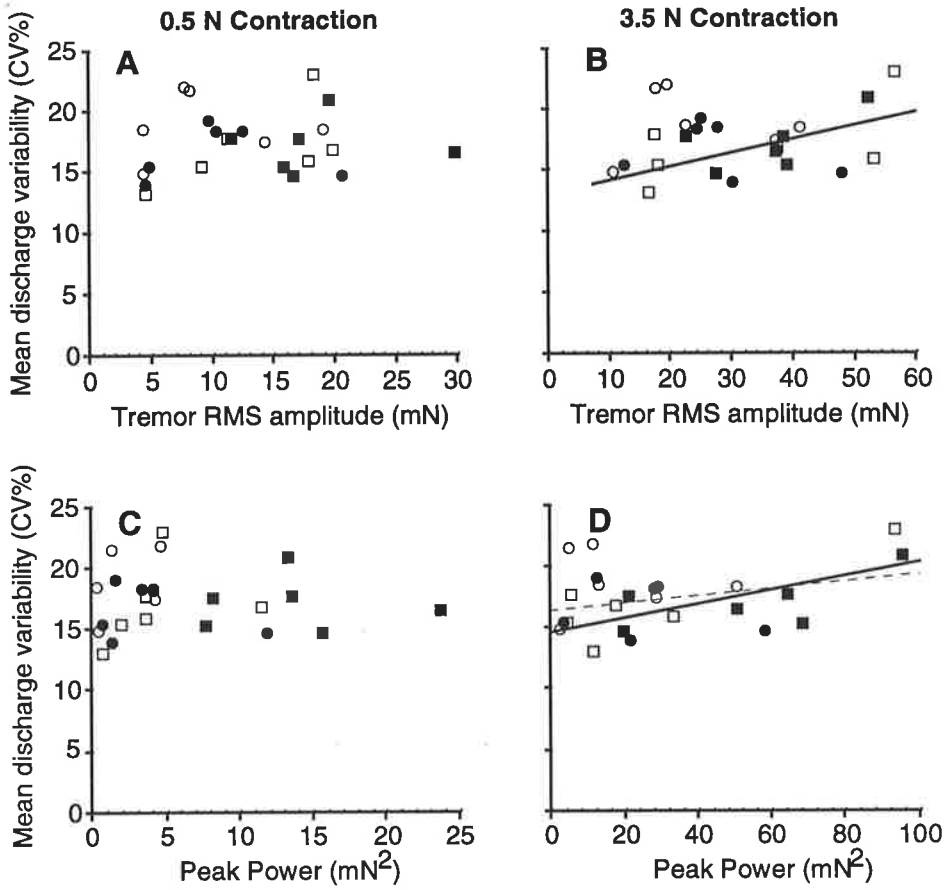

Figure 2.8 Relationships between motor unit discharge variability and force tremor in first dorsal interosseous.

Pooled data from all subjects showing the mean CV of ISIs for MUs in each FDI muscle plotted against the tremor RMS amplitude during isometric abduction of the index finger at 0.5 N (***A***) and 3.5 N (***B***). Fitted line in B is significant correlation for RH subjects alone (r^2 = 0.39). C, D, Mean MU CV is plotted against the peak power in the force frequency spectrum during isometric abduction of FDI at 0.5 N (***C***) and 3.5 N (***D***). Fitted lines in D show significant correlations for the entire population (dashed line, r^2 = 0.18) and for RH subjects alone (solid line, r^2 = 0.50). Unfilled squares: dominant hand, RH subjects; filled squares: non-dominant hand, RH subjects; unfilled circles: dominant hand, LH subjects; filled circles: non-dominant hand, LH subjects.

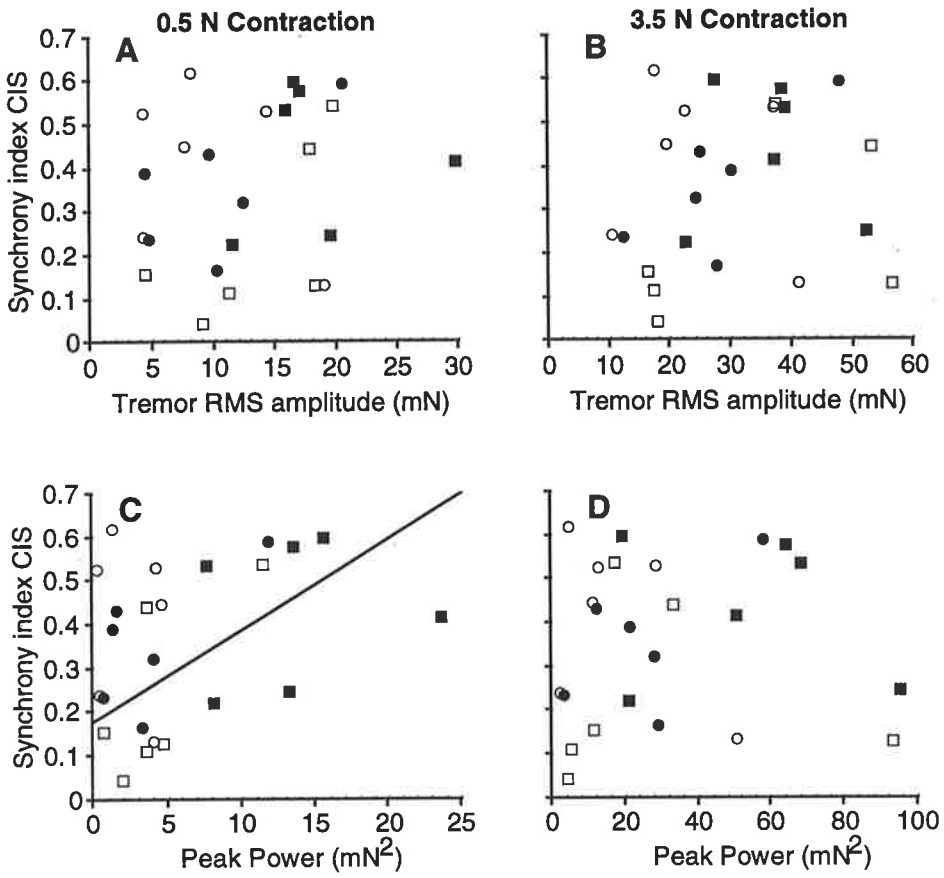

Figure 2.9 Relationships between the mean strength of motor unit synchronization and force tremor in first dorsal interosseous.

Pooled data from all subjects showing the mean motor unit synchronization strength (CIS) for each FDI muscle plotted against the tremor RMS amplitude during isometric abduction of the index finger at 0.5 N (***A***) and 3.5 N (***B***). CIS is plotted against the peak power in the force frequency spectrum during isometric abduction at 0.5 N (***C***) and 3.5 N (***D***). Symbols as in Fig. 2.8. The only significant correlation between MU synchronization and tremor was for RH subjects (squares) with the peak spectral power during the 0.5 N contraction (fitted line shown in C; $r^2 = 0.35$).

in the non-dominant hand of RH subjects had relatively more power at the peak frequency, and 3) MU discharge variability and synchronization had only a weak effect on the magnitude of tremor.

2.4.1 MU discharge properties and handedness

No differences existed in discharge rate or variability in FDI MUs in the dominant and non-dominant hands. Schmied *et al.* (1994) found that firing rates of ECR MUs tended to be lower in the preferred arm, but also found no differences in discharge variability between hands. In the FDI it seems that discharge properties of individual motoneurons were not influenced by preferred use of the hand.

The incidence and strength of MU synchronization, however, were significantly reduced in the dominant hand of RH subjects to about 60% of that seen in the contralateral hand, and in either hand of LH subjects. Differences in RH subjects were consistent; significant differences in synchrony between hands were seen in four of six individuals. The two RH subjects with non-significant differences in MU synchrony between hands had above-average LQ values for right-handers (0.81 & 1.00), so the differences in synchrony were not simply related to the stated degree of hand preference using this questionnaire. Questionnaires are a less precise measure of laterality differences than tests of hand skill (Provins & Magliaro, 1993). The similarity of MU synchronization between hands in LH subjects is consistent with their displaying less lateralisation than RH subjects in skilled use of the hand using tests such as writing (Provins & Magliaro, 1993).

The reduced incidence and strength of FDI MU synchronization in the dominant hand of RH subjects was opposite to the expected result. The most important cause of narrow peaks in the cross-correlogram is presumably the direct corticospinal projection (Farmer *et al.* 1990; Datta *et al.* 1991), and it is known that single CM cells have monosynaptic connexions with a large proportion of motoneurons in their target muscles (see Lemon, 1993). It was expected that MU synchronization would be more prominent in the dominant hand for three reasons. The first was a circumstantial association, based on the importance of

monosynaptic connexions from motor cortex to motoneurons for skilled, independent use of the digits (see section 1.3.3). Second is the anatomical finding in man that the corticospinal tract is larger on the right side of the body in 75% of individuals, with the average R:L ratio of areas being 3:1 (Nathan *et al.* 1990). Interestingly, asymmetry of the pyramidal tracts is apparently not related to handedness (Kertesz & Geschwind, 1971). It was expected that the much higher number of corticospinal tract fibres to the right side would mean a more effective input from motor cortex to right hand muscles, and thus higher MU synchronization. It is not clear what this anatomical finding would mean for LH subjects. It is not known, for example, what proportion of corticospinal tract fibres going to each side arise from CM cells, providing monosynaptic projections to motoneurons. Third, the notion that direct motor cortical inputs to motoneurons are more effective in the dominant hand is supported by the finding that the threshold for activation of APB by TMS is lower for the hemisphere activating the dominant hand in both LH and RH subjects (Triggs *et al.* 1994). The motor cortical representation of the hemisphere controlling the dominant hand using magnetoencephalography is larger during index finger abduction compared to the opposite hemisphere during non-dominant index finger abduction (Volkmann *et al.* 1996). Increased specialised use of a finger in Braille readers can also enhance motor cortical representation of muscles in the reading finger (Pascual-Leone *et al.* 1993). In summary, the available evidence points to a stronger projection from motor cortex to motoneurons of the dominant hand. Assuming no differences in synaptic efficacy or projection frequency to individual motoneurons within the motor pool, this would be expected to result in higher MU short-term synchronization in the dominant hand.

Schmied *et al.* (1994) found that the incidence and strength of MU synchrony in ECR was higher in the preferred arm of both RH and LH subjects, presumably reflecting a stronger direct input from branched CM cell axons to ECR motoneurons in the preferred arm. Although LH subjects show less lateralisation during skilled task performance such as hand writing (Peters & Servos, 1989; Provins & Magliaro, 1993) the finding of stronger MU synchronization in the dominant arm of LH subjects by Schmied *et al.* (1994) may be related to the notion that the results were not obtained during the performance of such a task. A

greater ability for fractionated control of individual muscles distinguishes the muscles controlling the fingers from the wrist muscles studied by Schmied *et al.* (1994), and the lateral corticospinal tract inputs are essential for this fine control (Kuypers, 1981; Bortoff & Strick, 1993). The present finding of reduced MU synchronization in the dominant hand of RH subjects seems unlikely to be due to a reduced number or efficacy of corticospinal inputs to the FDI motor pool. There seem two possibilities to explain the present findings. The first is that individual CM cells have monosynaptic connections with a smaller proportion of motoneurons within the FDI motor pool in the dominant hand of RH subjects. This idea is supported by the findings of Mills & Schubert (1995), who suggested that the corticospinal fibres activated by TMS do no influence MU synchronization and therefore are of limited divergence. It is in independent control of fine finger movements that the largest skill differences between hands are apparent, and it may be that a more restricted distribution of inputs from single CM cells to motoneurons within a single muscle controlling the digits is one of the physiologic processes underlying skilled use of the fingers. A corollary for skilled use of the fingers might be a strengthening of branched CM cell inputs to motoneurons of different, synergistic muscles. The second possibility is that the CM cells were less active when the task was performed by the dominant hand in RH subjects. Task-related differences have been reported in CM cell excitability (Datta *et al.* 1989) and MU synchrony (Bremner *et al.* 1991c). There are no objective data on these possibilities from animal studies, but they are potentially testable in non-human primates with current techniques (recently reviewed by Lemon, 1993).

No correlation was found between synchrony and discharge variability in the present study (Fig. 2.5B), although this has been reported previously in FDI (Nordstrom *et al.* 1992) and for the non-preferred arm only in ECR (Schmied *et al.* 1994). The present findings suggest that the relationship between MU synchrony and discharge variability is not particularly robust. MU CV was not different between hands in FDI (present study) or ECR (Schmied *et al.* 1994), and there were no differences in mean MU discharge rates between hands in FDI. The reduced MU synchronization in the dominant hand of RH subjects can therefore not be attributed to the discharge patterns of individual MUs. Similarly, the synchrony index

CIS was not related to the discharge frequency of the MUs contributing to the cross-correlogram (Fig. 2.5A), which is in agreement with the findings of Nordstrom *et al.* (1992).

MU synchrony was not only weaker in the dominant hands of RH subjects, but the cross-correlogram peaks were wider by some 4-6 ms than those in LH subjects, and the non-dominant hand of right-handers. This is consistent with the weaker narrow short-term synchronization, so that broader correlations were relatively more prominent in these pairs. One issue which complicates this finding is that the width of the central peak is usually much more difficult to assess in cross-correlograms with weak MU synchronization. Nevertheless, wider peaks that are believed to reflect synchronization of the common input pathways (Kirkwood *et al.* 1982) were also observed in the dominant ECR muscle by Schmied *et al.* (1994). These findings suggest that when the muscles are used preferentially in everyday tasks there is a greater contribution to MU synchronization from synchronized presynaptic inputs. A reduction in the effectiveness of the direct corticospinal input may modify the influence of spinal interneurons, producing a broader central peak in the cross-correlogram as has been observed following spinal cord lesions in the anaethetised cat (Kirkwood *et al.* 1982; Kirkwood *et al.* 1984). However, as is usual for FDI, broad central peaks (> 40 ms) were very rare (only 1 significant peak > 40 ms). Only 7% (16/266) of significant peaks were wider than 25 ms, and no hand in any subject had a mean width of significant peaks greater than 24 ms. In the ECR muscle, broad duration peaks were obtained when one or both MUs of the pair were high threshold, fast contracting MUs (Schmied *et al.* 1994). This finding could not be verified in the present study, as only a small range of MU recruitment thresholds were examined (most < 1 N).

2.4.2 Mechanisms of tremor generation

Mechanisms of tremor production include interaction between firing patterns of MUs (firing rates, variability and independence of discharge) that are transduced into mechanical events by the muscle, mechanical properties of the extremity, segmental reflex mechanisms (which may reinforce mechanical oscillations), and oscillatory driving of MUs by some CNS

mechanism (reviewed by Stein & Lee, 1981). The relative importance of each of these mechanisms probably depends on the particular experimental arrangement. An important determinant of tremor in an isometric contraction is undoubtedly the partly fused twitches produced by the MUs that are discharging at sub-tetanic rates. Both experimental (Allum *et al.* 1978) and modelling (Christakos, 1982) studies show that the 6-12 Hz component of tremor is strongly influenced by the unfused twitch profile of the recently recruited MUs, which have the largest twitches (the size principle) and discharge in this frequency range. Differences in mean MU discharge rates (altering the relative twitch fusion), variability (Elek *et al.* 1991), and synchronous discharge (Allum *et al.* 1978; Christakos, 1982) may all influence tremor. A fourth aspect of MU discharge that may contribute to tremor is a common modulation of MU discharge rates at the tremor frequency (Elble & Randall, 1976) which may arise from a central or segmental oscillator, but this was not examined. It is important to note that the latter is not the same as MU synchronization, although that term has been applied to the phenomenon.

2.4.3 Handedness, MU discharge, and tremor

It was of interest to see whether force tremor varied systematically between dominant and non-dominant hands in LH and RH subjects, and if any features of the neural control of the muscles that were associated with differences in force tremor could be identified. The use of an isometric force task minimised a contribution to tremor from mechanical oscillation of the limb, which may not be related to neural events in the muscle (Elble & Randall, 1978). The FDI is easily activated in isolation at low forces and is the only muscle producing index finger abduction, thus the conditions were optimal for correlating differences in MU discharge properties with tremor.

There were no significant differences in peak tremor frequency between hands in LH or RH subjects (Fig. 2.7E,F). The peak frequency in the force spectra was between 6 and 7 Hz, which is consistent with most published data for FDI during isometric contraction, which show peaks in the 6-8 Hz range (Stephens & Taylor, 1974; Allum *et al.* 1978; Galganski *et al.* 1993). This is also the range of lowest tonic discharge rates for newly recruited FDI

MUs (Freund *et al.* 1975).

RH subjects had larger tremor (Fig. 2.7A) and relatively more power at the peak spectral frequency in the non-dominant hand (Fig. 2.7C) during the low-force contraction only. This trend in the present results is similar to the recent report by Löscher & Gallasch (1993) who found larger tremor in the non-dominant hand of RH subjects during isometric power grip over a range of forces. Differences between hands were not consistent in the present study, however, as none were seen at the higher force level. Isolated contraction of FDI at low forces and a power grip may not be comparable tasks. Marsden *et al.* (1969b) found no significant differences in finger tremor between hands, but their results are not directly comparable because the subjects were supporting their outstretched index finger against gravity, with the hand unsupported.

The absence of a clear and consistent effect of handedness on tremor is consistent with the similarities of the MU discharge properties (mean ISI and CV) in all groups (Table 2.1). Discharge variability (CV) was the only MU parameter to show a significant correlation with tremor using pooled data from all subjects (Fig. 2.8D), yet this weak correlation was related to the distribution of power over the frequency spectrum, and was not significant in the 0.5 N contraction. There was a significant correlation between CV and tremor RMS amplitude for RH subjects in the 3.5 N contraction (Fig. 2.8B), but this was still rather weak (r^2 = 0.39). MU synchronization was lower in the dominant hand of RH subjects, which theoretically would be expected to reduce tremor (Christakos, 1982), however, it was found that correlations with tremor were weak (see below). In the absence of relevant differences in MU discharge properties, the explanation for differences in tremor between hands at the low target force may be differences in size or contractile speed of MU twitches (Allum *et al.* 1978; Christakos, 1982). Mean (± S.D.) maximal voluntary abduction forces of the index finger were similar in dominant (45 ± 11 N) and non-dominant (41 ± 7 N) hands (paired t-test, $P > 0.05$), suggesting no major differences in muscle strength. Tanaka *et al.* (1984) have reported that the twitch time-to-peak is slower in the FDI of the dominant hand (60 *vs.* 69 ms). If such a difference exists in the MUs recruited at low forces, this might explain the

tendency to larger tremor in the non-dominant hands of RH subjects at the low target force as the individual MU twitches would be less fused at comparable MU discharge rates.

2.4.4 MU synchronization and tremor

The role of MU synchronization in tremor generation is poorly understood. One problem is that the term synchronization has been used rather loosely to encompass any correlated firing behaviour of MUs, such as the appearance of rhythmic oscillations in surface EMG amplitude (Lippold *et al.* 1957; Elble & Randall, 1978; Stiles, 1980), and common modulation of MU firing rates (Elble & Randall, 1976) at the tremor frequencies. These phenomena contribute to tremor, but they do not necessarily indicate a tendency for *synchronous* MU discharge (Taylor, 1962). Nevertheless, the prevailing view is that MU synchronization is an important contributor to tremor.

Experimental (Dietz *et al.* 1976; Allum *et al.* 1978) and modelling studies (Christakos, 1982) have suggested that MU synchronization is not necessary for tremor, although increasing MU synchronization experimentally by stimulation (Allum *et al.* 1978) or in the model (Christakos, 1982) increased tremor amplitude. The relationship between MU synchronization and tremor has only been examined directly in two previous studies, with conflicting results (Dietz *et al.* 1976; Logigian *et al.* 1988).

The present data suggest that the weak MU synchronization displayed by normal subjects in FDI is not an important determinant of finger tremor. Correlations between MU synchrony and tremor were weak, and non-significant with one exception (Fig. 2.9). These findings are in agreement with the results of Logigian *et al.* (1988), who studied ECR MUs (19 MU pairs in three subjects) and wrist tremor. The observation that synchronous discharges in different pairs of MUs are not correlated in time (Dengler *et al.* 1984; De Luca *et al.* 1993) means that force fluctuations associated with synchronous events are randomly dispersed in time, which minimises their influence on tremor force fluctuations.

These results are in some conflict with those of Dietz *et al.* (1976), who found a positive correlation between MU synchrony and tremor amplitude that was significant in

gastrocnemius/soleus, but not in FDI. Dietz *et al.* (1976) had a relatively small sample of MUs (16 pairs in FDI and 22 in gastrocnemius/soleus). It is now known that there are large differences in the strength of synchrony in different MU pairs in a single muscle during the same task (Bremner *et al.* 1991b; Nordstrom *et al.* 1992), which means that it is necessary to sample from a large number of MU pairs to assess reliably the overall extent of MU synchrony in a muscle. In the present study, I optimised the conditions for assessing MU synchrony by using more subjects than Dietz *et al.* (1976), a larger MU sample per muscle (mean of 15 pairs *vs* 3-4), longer duration spike trains (3-5 min *vs* 30 s) to reduce variability in the synchrony measures, and an index of synchrony based on peak area which is more reliable than the single-bin measure used in early studies.

Unlike the Dietz *et al.* (1976) study, the tremor and MU recordings from the present study were not obtained in the same experimental session. The task performed in each case was effectively a constant-force isometric abduction of the index finger under visual control. Although tremor amplitude can vary between sessions, the standard deviation is 50% of the between-subject variation (Allum *et al.* 1978), and clear between-subject differences can be found for MU synchrony (Nordstrom *et al.* 1992) and tremor (Halliday & Redfearn, 1958; Elble & Randall, 1976). Sessional differences in estimates of FDI MU synchrony within subjects are much less than between-subject differences (M.A. Nordstrom, personal communication). While sessional differences may have reduced the correlations, it is unlikely that they would have obscured them altogether. The present results show that muscles with higher MU synchrony had no significant tendency to have larger force tremor.

MU synchronization has been shown to play a role in drug-enhanced tremors (Logigian *et al.* 1988), but the broad-peak synchrony operating under those conditions is clearly distinct from the narrow short-term synchrony seen in FDI under normal conditions. The present results support the suggestion that MU discharge variability and short-term synchronization have only a weak influence on the magnitude of physiological force tremor in normal subjects (Christakos, 1982; Logigian *et al.* 1988). The only significant difference in MU discharge properties of preferred and non-preferred hands was a reduced MU

synchronization in the dominant hand of right handers. This may reflect a reduced divergence of single CM cell inputs within the FDI motoneuron pool, or alternatively a reduced activation of CM cells controlling FDI during the index finger abduction task with their dominant hand. These differences may be associated with prolonged preferred use of that hand, but have a minimal effect on the tremor force fluctuations.

CHAPTER 3

RELATIONSHIP BETWEEN MOTOR UNIT SHORT-TERM SYNCHRONIZATION AND COMMON DRIVE

3.1 Introduction

The discharge of voluntarily activated human MUs is not completely independent. Two examples of correlated discharge patterns that can be demonstrated in pairs of concurrently active MUs in many muscles are short-term synchronization (the greater than chance tendency for concurrently active MUs to discharge within a few milliseconds of each other) and common drive (simultaneous fluctuations in mean discharge rate). MU short-term synchronization is believed to arise from the joint occurrence at the motoneurons of unitary EPSPs from branched axons of common pre-synaptic neurons (Sears & Stagg, 1976; Datta & Stephens, 1990). These highly correlated post-synaptic potentials generated by a proportion of the inputs to the tonically active motoneurons slightly increases the probability that they will discharge at the same time. A number of neuronal classes that project with wide divergence within the motoneuron pool may potentially contribute to MU short-term synchronization. In recent years, evidence has accumulated that inputs to motoneurons from the contralateral motor cortex are important for the generation of MU short-term synchronization (Farmer *et al.* 1990; Datta *et al.* 1991; Farmer *et al.* 1993a; Farmer *et al.* 1993b). The CM cells, which have widely divergent monosynaptic excitatory connections with motoneurons (reviewed by Porter & Lemon, 1993), seem likely to be the most important source of inputs responsible for MU short-term synchronization (see section 1.4.3).

Concurrently active MUs exhibit an in-phase, 1-2 Hz common modulation of mean

discharge frequency which has been termed "common drive" (De Luca *et al.* 1982b). This phenomenon, which is revealed by smoothing the time-varying firing rate over several successive discharges, is distinct from short-term synchronization which is the result of simultaneous shifts in discharge times in both MUs on a spike-by-spike basis. The mechanisms that may give rise to common drive have not been elucidated experimentally. Common drive presumably reflects a rhythmic 1-2 Hz modulation of activity in a population of last-order neurons. Widely divergent inputs to motoneurons from last-order neurons (i.e., the same mechanism that is believed to produce short-term synchronization) could be responsible for common drive, although recent evidence suggests that MU synchronization and MU coherence are not related (Mills & Schubert, 1995). However, in the genesis of common drive, the simultaneous arrival of unitary post-synaptic potentials at the motoneurons which is believed to promote synchronous discharge is less important than the effectiveness of the widely divergent inputs in transmitting slow fluctuations in the net excitatory drive simultaneously to a large proportion of the motoneuron pool. In theory, single last-order neurons need not have widely divergent inputs to the motoneuron pool to produce common drive; oscillatory activity that is highly correlated in a population of last-order neurons might be sufficient to produce common drive in the mean discharge rates of active MUs even if the motoneurons share few inputs from single last-order neurons.

In the present study I have examined the relative importance of the branched-axon inputs to motoneurons, which are recognised as important for the generation of short-term synchronization, for the genesis of common drive fluctuations in mean firing rate. This was studied by comparing, for a number of MU pairs in different subjects, the strength of MU short-term synchronization and the strength of the common drive fluctuations in their mean firing rates. The two analyses were performed on MU spike-train data from FDI muscle obtained during a single trial (1-5 min duration) of weak isometric abduction of the index finger. It was expected that if widely divergent, branched-axon inputs to motoneurons were important mediators of the common drive phenomenon, there would be a strong positive correlation between the strength of MU short-term synchronization and the common drive cross-correlation coefficient in MU pairs. As CM cell activity is believed to be important for

MU synchrony, this approach also gives information about the importance of CM cell activity for the generation of common drive.

3.2 Methods

The experiments were approved by the Committee for the Ethics of Human Experimentation at the University of Adelaide. Data are reported from 77 pairs of concurrently active MUs recorded in FDI muscle of 17 neurologically normal subjects (ages 18-47 years) who volunteered to participate in the study. The data were obtained as part of a larger study of the effects of training on MU discharge patterns (Chapter 4), and this subset comprises data from those pairs of MUs that could be discriminated with close to 100% accuracy (necessary for common drive analysis) and for long (1-5 min) epochs of tonic discharge (necessary for reliable short-term synchronization analysis). Three subjects (14 MU pairs) were musicians and four others (21 MU pairs) regularly lifted weights, while the remainder (5 LH subjects, 28 MU pairs; 5 RH subjects, 14 MU pairs) reported no special use of their hands. FDI MU pairs were obtained from dominant (34 pairs) and non-dominant (43 pairs) hands, with the degree of hand dominance determined by the Edinburgh handedness inventory (Appendix A).

3. 2. 1 Experimental apparatus

MU activity was recorded with two separate fine-wire electrodes inserted percutaneously into the FDI. Each electrode consisted of three Teflon-insulated fine wires (45 μm core diameter) threaded through the lumen of a 25-gauge disposable needle. The surface EMG of the left and right FDI was recorded with bipolar Ag-AgCl electrodes. Myoelectric signals were amplified (1000x), filtered (bandwidth 2 Hz-10 kHz) and recorded on FM tape (Vetter model 400D, Rebersburg, PA, USA, 22 kHz/ch) for off-line analysis. The index finger abduction force signal (bandwidth 0-5 kHz) was also recorded on tape.

Subjects were seated with their arm and hand secured in a manipulandum, the details of

which have been described in Chapter 2. The distal interphalangeal joint of the index finger was aligned with a load cell which measured the force of abduction. The manipulandum was designed so that abduction of FDI against the load cell involved only the index finger. To begin the experiment, subjects performed a steady, low-force, isometric abduction of the index finger. A single MU was chosen by the experimenters for the subject to control at a comfortable discharge rate (feedback unit). Subjects were provided with audio and visual feedback of the discharge times of the selected MU on an oscilloscope screen. The subject's task was to control the mean firing rate of the feedback unit at a constant level for 1-5 min. The activity of additional MUs was monitored during the trial to confirm that discriminable MU potentials were present in each channel for off-line cross-correlation. The procedure was repeated following repositioning of both electrodes, in order to sample from as many different MUs as possible.

3.2.2 Analysis

The procedure for MU discrimination was similar to that described in Chapter 2. Single MUs were discriminated using a computer-based template-matching algorithm (SPS 8701; *Signal Processing Systems, Prospect, S.A., Australia*). Action potentials belonging to a particular MU were identified on the basis of waveform shape, and great care was taken to confirm the discrimination accuracy. ISIs of identified MUs were measured (± 250 μs resolution) using an in-built function of the SPS 8701 and stored on computer. With the aid of ISI histograms, which were constructed from the discharge times of each MU, ISI records were scrutinised for every trial and each discriminated MU to assess discrimination accuracy. Abnormally short and long ISIs that were clearly the result of discrimination error (see Chapter 2) were noted, and files with discrimination errors greater than 1% of total discharges were not analysed further for the present study. Files satisfying this criterion for discrimination accuracy that could be paired with another containing ISIs from a concurrently active MU (recorded from a separate electrode) were reanalysed on a spike-by spike basis with the operator manually identifying unclassified spikes (usually superimpositions with other active MUs) using the off-line spike-sorting facilities of the SPS 8701. The resulting

file of MU discharge times contained close to zero incorrect ISI values due to discrimination error. An example of ISI *vs.* time plots from files used for the analyses is shown in Fig. 3.1A,B.

3.2.2.1 MU synchronization cross-correlograms

The cross-correlation histogram of the individual discharge times of each MU was used to determine the degree of MU short-term synchronization. This technique has been described in detail in Chapter 2. An example of a cross-correlogram is shown in the lower trace of Fig. 3.1C for the MU pair whose ISI *vs.* time plots appear in Fig. 3.1A,B. Cross-correlation histograms were restricted to periods in which both units of the pair were tonically active. Histograms with a mean bin-count < 4 were not analysed further. The position and duration of the synchronous peak (dotted vertical lines in Fig. 3.1C) was judged visually through the use of the CUSUM (Ellaway, 1978). The significance of synchronous peaks in the cross-correlogram was assessed using the method described by Wiegner & Wierzbicka (1987). A standard peak width of 11 ms, centred at time zero, was used for the quantification of MU synchronization in the MU pair if no significant peak was identified. The strength of MU synchronization was quantified by the synchrony index CIS, which is the frequency of extra synchronous discharges in the MU pair (i.e. the number of synchronous action potentials in the MU pair in excess of chance (dark area in Fig. 3.1 C) divided by the duration of the trial). For the accepted MU pairs, trial durations ranged from 53 - 265 s.

3.2.2.2 Common drive cross-correlation functions

Common drive analysis for the MU pairs was performed using spike-train data obtained from the same 1-5 min trial of isometric index finger abduction used for the synchronization analysis. It was not possible to use the spike-train data from the entire trial for common drive analysis (as was done for the synchronization analysis) because of the memory intensive nature of the computations involved. It was also not feasible to assess MU synchronization over a 5-s time period as for common drive, as MU synchronization needs a

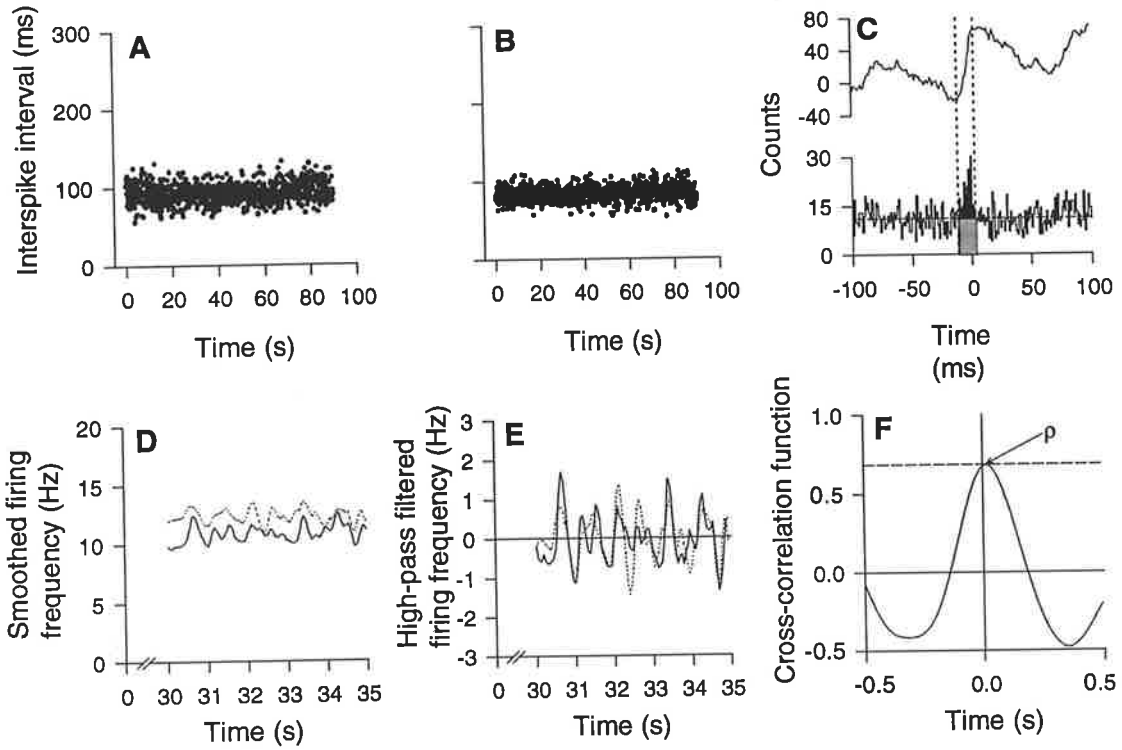

Figure 3.1 Quantification of motor unit synchronization and common drive in the same motor unit pairs.

A,B ISI *vs.* time plots for two concurrently active MUs. Mean ISI was 92.5 ms for the MU in A, and 83.2 ms for the MU in B. The duration of the trial was 89.7 s. Note the absence of abnormally short or long ISIs, indicating very accurate MU discrimination. ***C***, lower trace shows the cross-correlogram of the individual discharge times of MUs shown in A and B. The position and duration of the synchronous peak (vertical dotted lines) was judged visually from the cumulative sum (upper trace). The width of the peak was 15 ms centred at t = -4 ms. The mean bin count of off-peak bins in the cross-correlation histogram was 11.1 (dashed horizontal line). This value served to distinguish the counts expected due to chance (light-shaded area) from those counts in excess of chance (dark-shaded area) in the region of the synchronous peak. The synchrony index CIS for this MU pair was 0.98 s^{-1}. ***D***, a 5-s epoch of the time-varying smoothed firing rates (using a 400-ms symmetric Hanning window digital filter) of the MUs shown in A (solid line) and B (dotted line). ***E***, the high-pass filtered (filter characteristics; $H(f) = 1 - (\sin \pi f)/ \pi f$ with a low frequency cut-off of 0.75 Hz) version of the smoothed firing rate data shown in D. ***F***, cross-correlation function of the data shown in E, revealing the extent of any underlying common variation in mean firing rates for lags of ± 0.5 s during the 5-s epoch. The common drive coefficient ρ for this MU pair was 0.69 at t = 12.5 ms.

large number of counts to be visible in the cross-correlogram. As a compromise, to obtain an estimate of common drive that was representative of the entire trial four 5-s epochs were randomly selected from each trial that contained periods of relatively stable firing rate and no evidence of discrimination errors in the raw ISI *vs.* time plots.

The method of common drive analysis was that described by De Luca *et al.* (1982b) and involved three steps, all of which were implemented on a Macintosh computer.

i) Construction of a continuous firing rate representing each of the unit discharge records (e.g., Fig. 3. 1D).

The discrete discharges of the MU were used as the instantaneous firing rate at those times. Cross-correlation analysis however requires construction of a time-continuous representation of (mean) firing rate using an averaging window. This was performed by passing an impulse train representation of the MU discharges through a time-symmetric, non-causal Hanning window digital filter (using a sample interval of 0.25 ms, based on the spike discriminator's resolution). The standard width of 400 ms was used as an appropriate compromise in smoothing and was used for comparison with previous work (De Luca *et al.* 1982).

ii) High-pass filtering so as to consider the fluctuations in each of the firing rates (e.g., Fig. 3. 1E).

To remove the mean bias firing rates of each MU, another (digital time-symmetric, non-causal) zero-phase filter of the form:

$$H(f) = 1 - \frac{\sin(\pi f)}{\pi f} = 1 - \mathrm{sinc}(f)$$

is proscribed, having its low-frequency -3dB point at 0.75 Hz. This was directly implemented in the frequency domain by multiplication with the Fourier transformed firing rate records. By buffering the analysis epoch by 0.5-s each side (which is subsequently dispensed with) the problem of the circular convolution is avoided. Thus the manner in which the firing rates vary about their respective offsets is revealed.

iii) Cross-correlating the firing rates to determine a coefficient that measures their co-variation (e.g., Fig. 3. 1F).

To investigate common firing rate behaviour, a correlation function is evaluated:

$$r(i) = \frac{\sum_{j=0}^{n-i-1} x(j+i).y(j)}{\sqrt{\left(\sum_{k=0}^{n-1} x(k)^2\right)\left(\sum_{k=0}^{n-1} y(k)^2\right)}}.$$

This function is evaluated over a ± 0.5 s range of lead/lag intervals encompassing well beyond the ± 50 ms range used by other investigators which conventionally includes the maximum cross-correlation function (Kamen *et al.* 1992). The maximum correlation in this range is presented (together with its respective interval) as the common drive correlation coefficient (ρ) for each analysis. The possible values of the firing rate cross-correlation function ranges between +1 (perfect positive correlation) and -1 (perfect negative correlation). Values near zero indicate that the firing rates of the MU pair are unrelated.

The calculation of the cross-correlation coefficient was then validated by constructing artificial discharge times of MU pairs with a common drive modeller written in the Labview programming language. This program allowed the user to construct MU discharge times based on selected variables such as the mean bias firing rate of each MU, the amplitude of the 1.5 Hz common modulation, the level of arbitrary drive to each MU, and the lead or lag time between the two MUs. With this technique, the accuracy of the common drive cross-correlation algorithm could be verified.

To provide an estimate of values of ρ that might indicate a significant common modulation of discharge rates, the common drive analysis was performed on fifty different 5-s epochs of firing rate data from MU pairs that were not concurrently active (i.e. their discharge was completely unrelated). The mean (± S.D.) common drive coefficient ρ calculated from these unrelated data was 0.13 ± 0.21. Positive ρ values for unrelated data are expected, because the cross-correlation function fluctuates around zero, whereas the *maximum* value of the cross-correlation coefficient was selected within the ± 50 ms peak region. Representative data from two MUs whose discharges are unrelated are shown in Fig. 3.2.

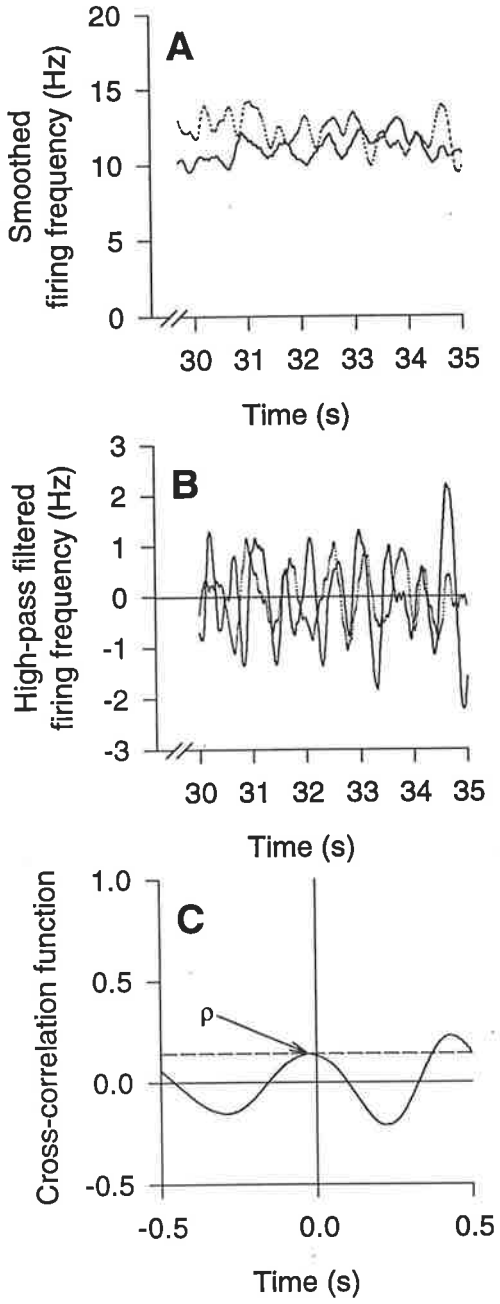

Figure 3.2 Representative example of common drive between the mean discharge times of two unrelated motor units.

A, a 5-s epoch of time-varying mean firing rates from two MUs during a constant force isometric contraction. The discharge times of each motor unit are taken from a separate contraction, and therefore are completely unrelated. ***B***, the high-pass filtered version of the smoothed firing rate data shown in A. ***C***, the resultant cross-correlation function of the data shown in B, revealing the extent of common drive behaviour between the two unrelated MUs. The maximum cross-correlation coefficient ρ for this MU pair between ± 50 ms was 0.14 at t = -3 ms.

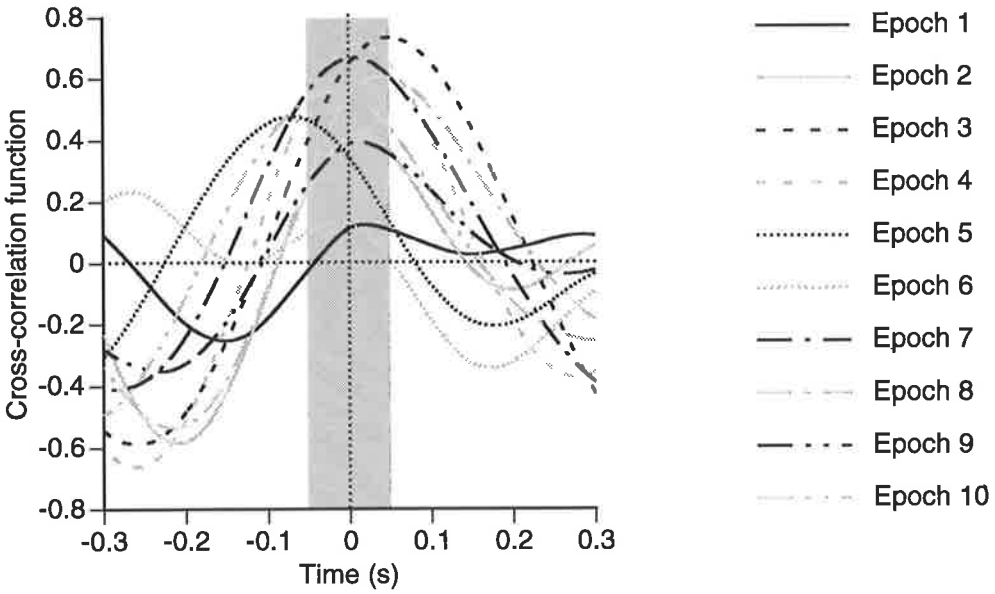

Figure 3.3 Example of the variability in the common drive cross-correlation function throughout the duration of a trial in one motor unit pair.

Data represents the common drive cross-correlation function for 10 consecutive 5-s epochs of isometric index finger abduction. The horizontal dotted line represents zero correlation between the mean firing rates of the two MUs. The vertical dotted line represents zero time lag between the common fluctuations in mean discharge rate of the two MUs. The common drive cross-correlation coefficient ρ is the maximum cross-correlation function between the two MUs within a $\pm$ 50 ms interval (indicated by the shaded area). In this motor unit pair, considerable variation exists in the value of ρ from one epoch to the next.

Previous studies have used only one 5-s epoch to quantify the common modulation of firing rates as it has been suggested that the epoch chosen for the analysis does not markedly affect the estimate of the common drive coefficient (De Luca & Erim, 1994). In the present study, it was found that estimates of the common drive coefficient from different 5-s epochs of data in the same MU pair had a CV of about 0.5. The high variability in the value of the common drive coefficient ρ for 5-s epochs during the duration of the trial is shown for one MU pair in Fig. 3.3. Due to this high variability, the ρ values obtained from the four 5-s epochs were averaged to improve the reliability of the estimate of the common drive coefficient for each MU pair.

3. 2. 3 Statistical Analysis

An unpaired t-test was employed for comparisons of MU synchronization index CIS and the common drive coefficient ρ between hands (dominant *vs.* non-dominant). Linear regression was used to assess the relationships between the MU synchronization index CIS and the common drive coefficient ρ in the same MU pairs. Significance was reported for $P < 0.05$.

3.3 Results

Forty-nine MU pairs (64%) had statistically significant peaks near time zero in the cross-correlation histogram. Mean width of the synchronous peak in the cross-correlograms for these pairs was 17 ms (range 9-37 ms). From all cross-correlograms, sixty-three MU pairs (82%) had a peak width less than 20 ms. Mean synchronization index CIS for all 77 MU pairs was 0.65 (range -0.16 to 2.97). Mean common drive coefficient ρ was 0.44 (range 0.03 - 0.74). Both measures of correlated MU discharge varied over a large range in different MU pairs.

For all MU pairs, there was no significant difference between the dominant (n=34 MU pairs) and non-dominant hand (n=43 MU pairs) for the mean (± S.E.) MU synchronization index CIS (dominant *vs.* non-dominant; 0.70 ± 0.10 *vs.* 0.61 ± 0.10) or the common drive

coefficient ρ (dominant *vs.* non-dominant; 0.44 ± 0.03 *vs.* 0.44 ± 0.02).

For all MU pairs, linear regression analysis revealed a weak but statistically significant positive correlation between the MU synchronization index CIS and the common drive coefficient ρ (fitted line in Fig. 3.4A, $r^2 = 0.06$, $P < 0.05$). Removal of the 14 MU pairs with a peak width greater than 20 ms slightly improved the correlation (Fig. 3.4B, $r^2 = 0.09$, $P < 0.05$). The linear regression correlation coefficients (Fig. 3.4) suggests that only about 6-9% of the variation in the strength of MU synchronization is associated with changes in the extent of common drive of firing rates. The weak interdependence of MU synchrony and common drive in the same MU pairs suggests that the two phenomena arise by relatively independent sources.

From the 49 cross-correlograms which showed a statistically significant peak, no relationship existed between the MU synchronization index CIS and the common drive coefficient ρ (Fig. 3.5A, $r^2 = 0.09$, $P > 0.05$). Similarly, no relationship existed between the synchrony index CIS and the common drive coefficient ρ for the significant synchronous peaks less than 20 ms in duration (Fig. 3.5B, $r^2 = 0.003$, $P > 0.05$, n=35).

3.4 Discussion

The strength of MU synchrony in FDI can vary considerably in different MU pairs in a single muscle, and there are even consistent differences between individuals (Bremner *et al.* 1991b; Nordstrom *et al.* 1992). I have made use of the wide range in strength of MU synchrony in different MU pairs to examine whether this property of MU discharge is linked with common drive of MU discharge rates.

The size and width of the central peaks in cross-correlograms of MU discharge found in the present study (mean 17 ms) are in agreement with the features of short-term synchronization reported previously in FDI (Datta & Stephens, 1990; Bremner *et al.* 1991b; Nordstrom *et al.* 1992). Short-term synchronization arises from the joint generation in the motoneurons of

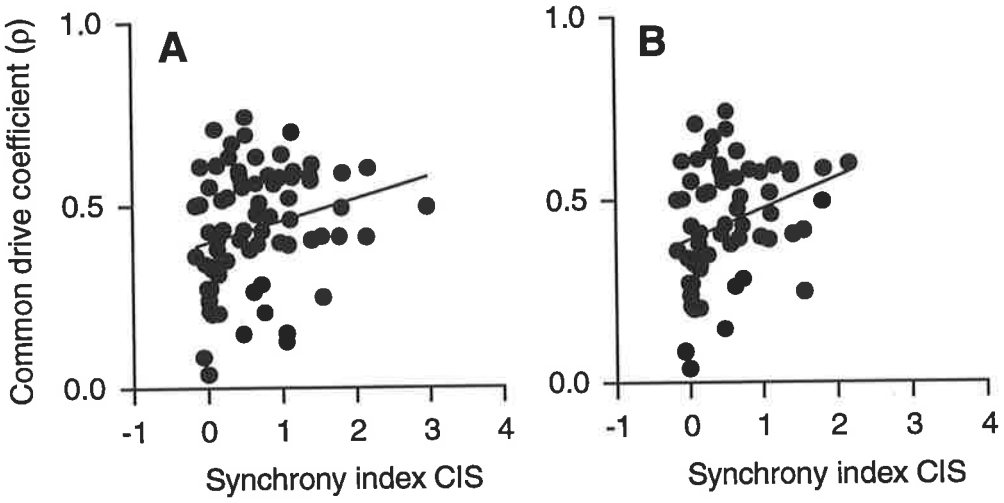

Figure 3.4 Relationship between the strength of motor unit synchronization and common drive in the same motor unit pairs.

A, Data from all MU pairs showing the synchronization strength (CIS) plotted against the common drive coefficient ρ for each MU pair. Linear regression (fitted line shown) revealed a weak positive correlation between these variables ($r^2 = 0.06$, $P < 0.05$). ***B***, Data as in A, showing the MU pairs with a synchronous peak less than 20 ms in width. Removal of the wider peaks slightly improved the relationship between synchronization strength and common drive coefficient (fitted line, $r^2 = 0.09$, $P < 0.05$).

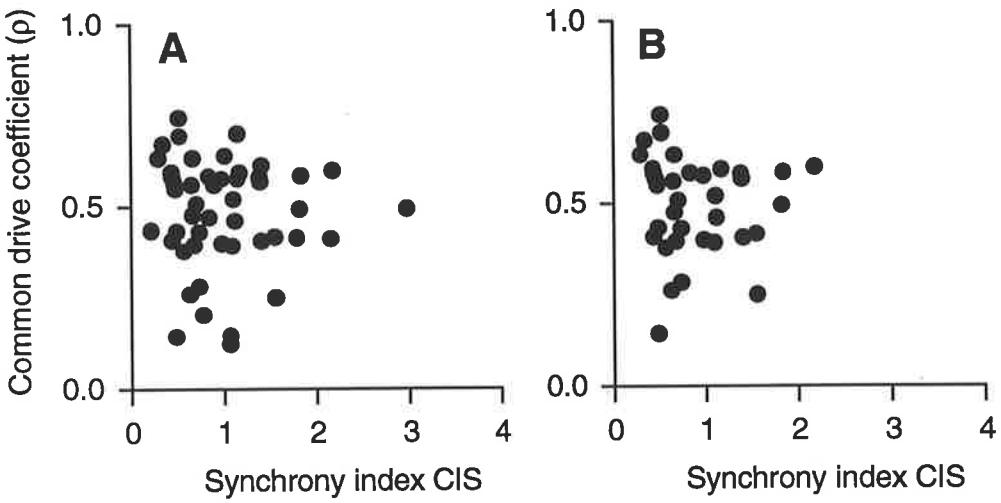

Figure 3.5 Relationship between the strength of motor unit synchronization and common drive in motor unit pairs with a significant synchronous peak.

A, Data from all MU pairs with a statistically significant synchronous peak showing the MU synchronization strength (CIS) plotted against the common drive coefficient ρ in each MU pair. ***B***, Data as in A, showing the MU pairs with a statistically significant synchronous peak less than 20 ms in width. Linear regression revealed no significant relationship between the strength of MU synchronization and common drive.

unitary EPSPs from branched axons of common pre-synaptic neurons (Sears & Stagg, 1976; Datta & Stephens, 1990), which slightly increases the probability that the motoneurons will discharge within a few milliseconds of each other. However, from the equations of Kirkwood & Sears (1978) only the narrowest central peaks of synchronization can be regarded as caused exclusively by a common pre-synaptic input. For peaks with broader duration's, synchronization of separate pre-synaptic inputs to the motoneurons must be contributing to the central cross-correlogram peak (Kirkwood *et al.* 1982; Kirkwood *et al.* 1984). As 82% of the cross-correlograms had peak widths less than 20 ms, it is likely that much of the observed MU synchronization was generated by activity in branches of common pre-synaptic fibres (see Datta & Stephens, 1990; Bremner *et al.* 1991b). Synchronization of separate presynaptic inputs have undoubtedly made some contribution to the central cross-correlogram peaks, but the peaks are relatively narrow, and the contribution is presumably small.

At least for intrinsic hand muscles, there is a body of evidence suggesting that CM cells from the contralateral motor cortex play a role in the generation of MU short-term synchrony. In primates the motor cortex CM cells have widely divergent monosynaptic excitatory connections with motoneurons in their target muscles (reviewed in Porter & Lemon, 1993). Supporting evidence for a corticospinal origin of short-term synchronization in man includes a gradient of MU synchrony in different muscles which matches the effectiveness of corticospinal inputs (Datta *et al.* 1991; Farmer *et al.* 1993a), and loss of short-term synchrony following lesions of the corticospinal pathway (Datta *et al.* 1991; Farmer *et al.* 1993b). Normal MU synchrony in a deafferented patient (Baker *et al.* 1988) supports a central origin. Evidence exists using TMS that differences in FDI MU short-term synchronization between hands are associated with hemispheric differences in activity of corticospinal neurons during the task (see Chapter 6). Probably the most convincing evidence, although pathophysiological, is the finding of strong MU short-term synchrony in concurrently active MUs in FDI muscles from opposite hands in a patient with mirror movements (Farmer *et al.* 1990). This is never seen in normal individuals. Using TMS, this patient was shown to have bilateral corticospinal projections to both FDI motoneuron

pools from the contralateral motor cortex.

Common drive is the simultaneous modulation of mean firing rates of the motoneurons during a voluntary isometric contraction which has a predominant frequency in the 1-2 Hz range (De Luca *et al.* 1982b). This low-frequency oscillation must be a feature of the net excitatory drive to the motoneurons, and could arise from the discharge patterns of last-order neurons with inhibitory or excitatory influences on motoneurons. If the oscillation is sufficiently strong in the population of last-order neurons, then the fluctuations in net excitatory drive will be effectively transmitted to the motoneuron pool even without wide divergence of axons from single last-order neurons. Although not essential, a high degree of divergence in the inputs to motoneurons carrying the common modulation in excitatory drive would tend to accentuate the common low-frequency modulation in firing rates of the motoneuron pool.

The source of the inputs producing common drive of MU firing rates has not been established. The low-frequency oscillation could be a feature of the descending command signal from supraspinal centres, or arise from the operation of segmental interneuronal circuits, or peripheral afferents. Several lines of evidence suggest a suprasegmental component in the generation of common drive. The nature of the task being performed under voluntary control influences the pattern of common drive seen following cross-correlation of firing rate fluctuations in MUs from antagonist muscles controlling flexion/extension of the interphalangeal joint of the thumb (De Luca & Mambrito, 1987). When the antagonists were coactivated so as to stiffen the joint, fluctuations in mean discharge rate were positively correlated at zero lag for MUs in the two muscles. In contrast, when a force tracking task was performed, fluctuations in mean discharge rate in MUs of the opposing muscles were negatively correlated at zero lag. The report that common drive is higher in FDI MUs from the dominant hand (Kamen *et al.* 1992) suggests a central origin, which may reflect lateral differences in supraspinal drive or operation of spinal interneuronal circuits. However, in the present study there was no tendency for common drive (or MU synchrony) to be influenced by hand preference. The present study may not be directly

comparable with Kamen *et al.* (1992) on this issue, as it included subjects who had trained their muscles for skill or strength, as well as untrained individuals. Evidence is presented in Chapter 4 indicating that the extent of MU synchrony is reduced in musicians, and increased in the strength-trained group. Untrained RH subjects have significantly lower MU synchrony in FDI of the dominant (skilled) hand, but this is not the case for LH subjects (Chapter 2), or in the trained groups. The inclusion of data from "skilled" hands in the present study is responsible for the lower incidence of synchrony (64%; see Chapter 4) compared to previous cross-correlation investigations in FDI (97%, Datta & Stephens, 1990; 88%, Bremner *et al.* 1991b).

Motor cortex CM cells, which have widely divergent monosynaptic projections to hand muscle motoneurons, and exert a powerful excitatory influence on them, are an obvious candidate for the generation of common drive. CM cells innervate multiple synergist muscles, and even project via interneurons to antagonist muscles (reviewed in Porter & Lemon, 1993), so they could potentially mediate the De Luca & Mambrito (1987) findings. A degree of synchronization is seen in the discharge of motor cortex neurons (Murphy *et al.* 1985), which include putative (Allum *et al.* 1982) and physiologically identified (Smith & Fetz, 1989) CM cells. Synchrony of motor cortex neurons raises the possibility that correlated discharge in the population of CM cells active during a task may produce an oscillation in net excitatory drive to motoneurons. Transient synchronous oscillatory activity has been seen in motor cortex neurons in the 25-35 Hz frequency band (Murthy & Fetz, 1991), but low-frequency (1-2 Hz) oscillations that might produce common drive have not been noted.

In the present study a weak positive relationship between the extent of MU synchrony and common drive was found in the same MU pairs in FDI (Fig. 3.4). As motor cortex CM cell activity is likely to be important for MU short-term synchronization, the relative independence of MU synchrony and common drive suggests that CM cells are not responsible for common drive of MU firing rates. This conclusion is supported by the results of Farmer *et al.* (1993a) who used both time- and frequency-domain analyses to

investigate correlated MU discharge in FDI. These authors found coherence between MU discharge rates in the 1-12 Hz and 16-32 Hz range. Coherence in the 1-3 Hz range was present in 25% of cases in which short-term synchronization was absent. Voluntary common modulation of MU firing rates at low frequencies (< 1 Hz) produced high coherence in the low frequency band without modifying short-term synchronization. Farmer *et al.* (1993a) concluded that MU coherence in the 16-32 Hz range was produced by the rhythmic discharge of the same inputs producing MU short-term synchronization, which are likely to be of corticospinal origin. MU coherence in the 1-12 Hz range was weakly associated with MU short-term synchronization, and likely to arise from activity in a separate pathway.

The low-frequency (1-2 Hz) modulation of MU firing rates must therefore arise from oscillatory activity in an indirect descending pathway, or segmental action of afferents or interneuronal circuits. Several possibilities acting at a segmental level do not seem to be important for common drive. The widely divergent, monosynaptic excitatory projections to motoneurons from muscle spindle Ia afferents are not necessary for common drive, as a muscle lacking muscle spindles (orbicularis oris inferior of the lip) has common drive of MU firing rates that is similar to that found in other muscles that contain spindles (Kamen & De Luca, 1992). Renshaw cell recurrent inhibition mediated by motoneuron axon collaterals is not essential for common drive, as the common drive phenomenon has been observed in masseter MUs (Nordstrom *et al.* 1986), and the trigeminal motor system lacks recurrent inhibition (Luschei & Goldberg, 1981). Recurrent inhibition is also thought to be weak in distal muscles of the upper limb (Rossi & Mazzocchio, 1992).

In summary, it was found that short-term synchronization and common drive of firing rates are relatively independent discharge properties of MU pairs. This dissociation suggests that wide divergence of inputs to motoneurons from single last-order neurons that give rise to MU synchrony (of which the corticospinal projection is a contributor) is not an important feature of the inputs giving rise to common drive. Common drive apparently arises from a population of last-order neurons whose discharge is sufficiently strongly entrained that

limited divergence does not prevent an oscillation in net excitatory drive being transmitted to the motoneuron population. While the identity and location of these neurons remains unclear, the present data suggest that widely divergent inputs from motor cortex CM cells are unlikely to play an important role in the generation of common drive of MU firing rates.

CHAPTER 4

MOTOR UNIT DISCHARGE AND FORCE TREMOR IN SKILL- AND STRENGTH-TRAINED INDIVIDUALS

4.1 Introduction

It is axiomatic that performance of the neuromuscular system is improved by training. There is an extensive literature on the physiological and biochemical changes in muscle fibres that underly the performance changes associated with strength and endurance training in particular (see Edstrom & Grimby, 1986 for a review). In contrast, much less is known about adaptations in neural control of muscles that accompanies training. It is evident that neural control factors play a role in the improved performance in strength-training (reviewed by Sale, 1987), but the nature of these adaptations is unknown. Skill-training undoubtedly is accompanied by altered neural control strategies, but at present the nature of these changes are ill-defined.

MUs are the smallest elements of neuromuscular control, and activation of MUs is the final common path for all neural control strategies. The principal aim of the present study was to establish whether skill- or strength-training practised over many years may influence discharge properties of MUs. If differences in MU discharge properties were found, it would be of interest to assess what these may reveal about altered neural control of the muscles, as well as the consequences for the involuntary force fluctuations (tremor) that limit the precision of force production. The group of skill-trained subjects were musicians who by practice over many years had developed the extraordinary control of their fingers required to play a musical instrument such as the piano. The strength-trained group was composed of individuals who had regularly engaged in high resistance weight-training of a number of

muscle groups for many years. This group had not specifically trained FDI muscle, but differences in neural control of FDI have been reported from a comparable group of strength-trained subjects (Milner-Brown *et al.* 1975).

Discharge properties of single MUs such as mean ISI and its CV influence the precision of force production by influencing involuntary force fluctuations (Christakos 1982; Elek *et al.* 1991). Differing muscle usage patterns may be the reason that mean discharge variability of FDI MUs in different untrained subjects varies over a two-fold range (Nordstrom *et al.* 1992). In the present study, MU short-term synchronization (Sears & Stagg, 1976; Datta & Stephens, 1990) and common fluctuations in mean firing rate ("common drive"; De Luca *et al.* 1982b) were also examined by cross-correlation of MU discharge times. These two distinct measures of correlated MU activity reveal information about the properties of last-order inputs to motoneurons. The lateral corticospinal tract is most likely important for MU short-term synchrony (Farmer *et al.* 1990; Farmer *et al.* 1993b), but seems to be less important for common drive (Chapter 3). Activity of corticospinal neurons underlies fine control of individual digits (for a recent review, see Porter & Lemon, 1993), and it is reasonable to assume that the operation of this pathway may be influenced by training. It was shown in Chapter 2 that MU synchrony is weaker in the dominant hand of RH subjects compared with their non-dominant hand, and both hands of left-handers. These results suggest that preferential use of the hand may influence cortical control of FDI in right-handers, who tend to have greater lateral differences in hand skill than left-handers (Provins & Magliaro, 1993). There is evidence that strength-training enhances MU synchronization, and this was attributed to strengthening of transcortical reflex pathways (Milner-Brown *et al.* 1975). It has been shown recently that the indirect method of estimating MU synchrony from the surface EMG used by Milner-Brown *et al.* (1975) has several limitations (Yue *et al.* 1995). For this reason MU synchrony was measured directly by cross-correlation of MU discharge times in strength-trained subjects.

It would be of interest in the present study to establish whether index finger tremor was different in the trained groups, and whether any difference could be related to differences in

FDI MU discharge properties. Differences in mean MU discharge rates (by altering the degree of twitch fusion), variability (Elek *et al.* 1991), synchronous discharge (Allum *et al.* 1978; Christakos, 1982), and common modulation of MU discharge rates (Elble & Randall, 1976) all may potentially contribute to the 6-12 Hz force tremor. In Chapter 2 it was found that differences in the overall extent of MU synchrony in FDI muscles could account for only about 6% of the variation in tremor amplitude during isometric index finger abduction. A criticism of that study is that MU discharge and tremor recordings were made in separate experimental sessions, and daily variation may have weakened any relationship between them. In the present study, comparisons of MU discharge properties and tremor were made with data obtained in a single experimental session.

Data from the control group of untrained RH subjects have been reported previously (Chapter 2). Data from some subjects in the present study were used with those of additional subjects in a comparison of the strength of MU synchronization and common drive in the same MU pairs (Chapter 3).

4.2 Methods

Sixteen healthy adults (ages 18-47 years) volunteered to participate in the study and gave informed consent to the procedures. The experiments were approved by the Committee for the Ethics of Human Experimentation at the University of Adelaide. The experimental groups consisted of five male weightlifters (denoted strength-trained subjects) who participated in strength-training activities on average 8 hrs/week for four years (range; 4-14 hrs/week, 2-6 yrs) and five musicians (skill-trained subjects; 2 males and 3 females) who played a musical instrument (involving independent use of the digits of both hands) on average 12 hrs/week for 8 years (range; 6-35 hrs/week, 6-10 yrs). Comparisons were made between the trained groups and six untrained subjects (all RH males) from Chapter 2. The degree of hand dominance was assessed by the Edinburgh Handedness Inventory (Appendix A; Oldfield, 1971). A LQ was calculated for each subject based on the answers to the

questionnaire, with a positive value indicating right-handedness and a negative value indicating left-handedness. Fifteen subjects were RH (mean LQ 0.9, range 0.5 - 1.0), and one skill-trained subject was LH (LQ = -1.0).

4. 2. 1 Experimental Arrangement

The experimental arrangement and recording procedures were similar to that described in Chapter 2. Briefly, the subject's right or left arm and hand was secured in a manipulandum. The force of abduction was measured by a load cell aligned with the distal interphalangeal joint of the index finger. The surface EMG of the left and right FDI was recorded with bipolar Ag-AgCl electrodes placed 2-3 cm apart. MU activity was recorded simultaneously with two separate fine-wire electrodes inserted percutaneously into the FDI. Myoelectric signals were amplified (1000x), filtered (bandwidth 2 Hz-10 kHz) and recorded on FM tape (Vetter model 400D, Rebersburg, PA, USA, 22 kHz/ch) for off-line analysis. The DC force signal was filtered (0 - 50 Hz) and digitised (1 kHz) on-line on a Macintosh computer. Force was also bandpass filtered (1 - 50 Hz) and amplified (5-10x) prior to recording.

4. 2. 2 Protocol

For the untrained control subjects, force tremor and MU synchronization recordings were obtained in three or more separate sessions (see Chapter 2). Tremor data obtained on two different days were pooled, to reduce sampling error due to daily fluctuations. These data were used in comparisons of tremor between groups in the present study. The sequence of tests in the trained subjects was constructed so that the issue of the relationships between MU discharge properties and tremor could be examined using data from a single session. Skill- and strength-trained subjects attended the laboratory on two occasions to assess force tremor and MU discharge properties. For these subjects, force tremor was assessed for both hands at the beginning of each session. Following this, MU activity was recorded from FDI of one hand. The other hand was used for MU recording in the other session on a different day. The tremor data from the two sessions were combined for comparison of tremor properties between the subject groups, as was done for the untrained control group. For

correlations between MU discharge properties and tremor, only the tremor values obtained on the day of the MU experiment were used in the comparisons, as these data may be more closely related to the MU discharge properties detected on that day. For this reason, data from untrained control subjects were not included in the comparison of tremor and MU discharge properties.

The procedure to assess force tremor was similar to that described in Chapter 2. Once secured in the manipulandum, the subject was required to produce a steady index finger abduction for 40 s at target forces of 0.5 and 3.5N, corresponding to approximately 2% and 11% of maximal force, respectively. These forces were chosen because they encompassed the range of forces seen in experiments in which the subject voluntarily controlled the discharge of an FDI MU at a steady, low rate (see below, and Chapter 2). Hands were tested in random order, with 1 min rest between trials, and the test sequence progressed from smallest to largest target force. The final test in each hand was maximal index finger abduction.

After the force matching trials, several intramuscular electrodes were inserted in the FDI of one hand, and subjects performed a steady, low-force, isometric abduction of the index finger. During MU recording, most contractions were in the range 0.1 N to 2 N, with no contraction over 4 N. The procedure for examining MU activity was described in Chapters 2 and 3. Briefly, a single MU from one intramuscular electrode was chosen by the experimenters for the subject to control at a comfortable discharge rate (termed the feedback MU). Subjects were given audio feedback of MU discharge, as well as visual feedback of mean discharge rate of the feedback MU on an oscilloscope screen. The subject's task was to control the mean firing rate of the feedback MU at a constant level for 1-5 min. Subjects rested for at least 2 min following each trial, and one or both electrodes were repositioned to sample from different MUs. Trials were repeated with each new combination of active MUs so that a large number of MUs were sampled in a single experiment.

4.2.2 Analysis

4.2.2.1 Force tremor

The high-gain force records from the force-matching trials were analysed according to the procedure detailed in Chapter 2. The high-gain force records were digitised (1 kHz sampling rate), and four 5-s epochs from the beginning of each 40-s trial were digitally filtered (5th order Butterworth, bandwidth 4-30 Hz). The RMS error of the filtered force records from each epoch were calculated, and the four values averaged to give an RMS error representative of the 40-s force-matching trial. The power spectral density function of the high-gain force signal was calculated using an FFT, using data from the same 5-s epochs used for the RMS error calculations. Spectra from different epochs were averaged in the frequency domain to provide the final power density spectrum representative of each force-matching task for each subject. The peak power in the force frequency spectrum and the peak tremor frequency were quantified from these force spectra. Data obtained on the day of the MU experiment were used for comparisons of MU discharge properties and tremor. Tremor data from two sessions were averaged to provide the data used for comparisons between subject groups.

4.2.2.2 MU discharge

All analyses were performed off-line from the taped records. Single MUs were discriminated using the SPS 8701, a procedure which has been described in Chapters 2 and 3. ISIs of identified MUs were measured (± 250 μs resolution) using an in-built function of the SPS 8701 and stored on computer. ISI histograms were constructed from the discharge times of each MU. Abnormally short and long ISIs that were clearly the result of discrimination error were excluded from statistical analysis (see Chapter 2). ISI files with >5% discrimination errors (usually missed spikes due to superimpositions) were excluded from all analyses. From the remaining MUs, the mean, standard deviation and co-efficient of variation (CV = SD/mean x 100) of the ISIs were determined using a commercially available statistical package (Statview II, Abacus Concepts).

ISI files created with the SPS 8701 were used to produce cross-correlation histograms of the discharge times of discriminated MUs to assess MU synchronization (Nordstrom *et al.* 1992)(see Chapter 2). This procedure is identical to that described in Chapters 2 and 3. The magnitude of a synchronous peak in the cross-correlogram was quantified using the synchronization index CIS, which is independent of the discharge rate of the MUs contributing to the cross-correlogram (Nordstrom *et al.* 1992).

Pairs of MUs exhibit a simultaneous modulation of mean discharge rates during their voluntary activation that has been termed "common drive" (De Luca *et al.* 1982b). Analysis of common drive of MU pairs was performed using spike train data from the same 1-5 min trial of isometric index finger abduction of FDI used to assess MU synchronization. Only MU data that contained periods of relatively stable firing rate and could be discriminated with close to 100% accuracy were selected for common drive analysis. To obtain an estimate of common drive that was representative of the entire trial, four randomly selected 5-s epochs that met the selection criteria were examined from each trial. A total of 80 MUs (49 MU pairs) were included in the common drive analyses. The technique of common drive analysis was described in Chapter 3. Briefly, the time-varying instantaneous discharge frequency of each MU spike train was smoothed using a 400 ms symmetric Hanning window digital filter. The smoothed firing rate records from each of the selected 5-s epochs were then digitally high pass filtered (filter characteristics; $H(f) = 1 - (\sin \pi f)/ \pi f$ with a low frequency cut-off of 0.75 Hz). The high-pass filtered firing rate records of the two concurrently active MUs were then cross-correlated to reveal the extent of any underlying common variation in mean firing rates for lags of ± 0.5 sec. The possible values of the firing rate cross-correlation function ranges between +1 (perfect positive correlation) and -1 (perfect negative correlation), with values near zero indicating that the fluctuations in mean firing rates of the MU pair are unrelated. The peak positive value of the firing rate cross-correlation function within ± 50 ms of time zero was termed the common drive coefficient (ρ). Four 5-s epochs were averaged to provide the final mean value of ρ for each MU pair.

4.2.3 Statistical Analysis

Data are presented as mean ± S.E unless otherwise stated. A two-way ANOVA was employed for comparisons between group (skill, strength and untrained) and hand (dominant, non-dominant). Dependent variables for comparison of MU discharge properties were mean ISI, coefficient of variation (CV), MU synchronization (CIS) and common drive coefficient (ρ). Dependent variables for tremor analyses were tremor RMS amplitude, peak power in the force frequency spectrum and tremor peak frequency. Significant effects for group and hand were analysed further with a one-way ANOVA and Scheffe's F test. Linear regression was used to assess the relationships between MU discharge properties and force tremor measures obtained in the same session. Significance was reported for $P < 0.05$.

4.3 Results

Discharge properties of individual MUs, as assessed from the mean ISI and the CV of the mean ISI, were similar in both hands of skill-trained, strength-trained and untrained subjects (Table 4.1). There were no significant differences in MU mean ISI or CV between the dominant and non-dominant hands in any of these groups (Table 4.1). There was a significant difference in MU mean ISI between the skill-trained (92.1 ± 1.1 ms, n = 165) and untrained (97.7 ± 1.6 ms, n = 183) subjects (Scheffe's F test, $P < 0.01$). Mean ISI for MUs in the strength-trained subjects was 94.3 ± 1.1 ms (n = 188). Mean CV for MUs was 18.6 ± 0.4 (165) in skill-trained subjects, 17.5 ± 0.3 (183) in untrained subjects, and 17.8 ± 0.3 (188) in strength-trained subjects. There were no significant differences in CV between groups.

Table 4.1. Summary of two-way ANOVA comparisons for training status and hand dominance.

	Effect		
Dependent variable	*GROUP (Skill-trained, Strength-trained, Untrained)*	*HAND (Dominant vs. Non-dominant)*	*Interaction*
MU discharge			
Mean ISI	F[2,530] = 4.9 P < 0.01	F[1,530] = 0.8 n.s.	F[2,530] = 2.2 n.s.
Mean CV	F[2,530] = 2.9 n.s.	F[1,530] = 0.1 n.s.	F[2,530] = 0.4 n.s.
Mean Synchronization index (CIS)	F[2,538] = 17.0 P < 0.001	F[1,538] = 1.2 n.s.	F[2,538] = 4.8 P < 0.01
Synchrony Peak Width	F[2,315] = 5.5 P < 0.01	F[1,315] = 3.2 n.s.	F[2,315] = 5.3 P < 0.01
Mean Common Drive Coefficient (ρ)	F[2,43] = 8.6 P < 0.001	F[1,43] = 0.8 n.s.	F[2,43] = 0.7 n.s.
Mean CIS (Common Drive pairs only)	F[2,43] = 8.6 P < 0.001	F[1,43] = 0.7 n.s.	F[2,43] = 0.8 n.s.
Force			
Tremor RMS (0. 5 N contraction)	F[2,26] = 3.9 P < 0.05	F[1,26] = 0.9 n.s.	F[2,26] = 0.4 n.s.
Tremor RMS (3. 5 N contraction)	F[2,26] = 6.1 P < 0.01	F[1,26] = 0.0 n.s.	F[2,26] = 0.1 n.s.
Peak power in the force frequency spectrum (0. 5 N contraction)	F[2,26] = 2.2 n.s.	F[1,26] = 1.9 n.s.	F[2,26] = 0.6 n.s.
Peak power in the force frequency spectrum (3. 5 N contraction)	F[2,26] = 3.9 P < 0.05	F[1,26] = 0.1 n.s.	F[2,26] = 0.7 n.s.
Peak tremor frequency (0. 5 N contraction)	F[2,26] = 0.5 n.s.	F[1,26] = 6.5 P < 0.05	F[2,26] = 1.0 n.s.
Peak tremor frequency (3. 5 N contraction)	F[2,26] = 2.0 n.s.	F[1,26] = 0.5 n.s.	F[2,26] = 0.9 n.s.
Index finger abduction MVC force	F[2,26] = 9.5 P < 0.001	F[1,26] = 0.4 n.s.	F[2,26] = 2.1 n.s.

4.3.1 MU synchronization and training status

Representative examples of cross-correlograms from the dominant and non-dominant hands of one skill-trained, one strength-trained and one untrained RH subject are shown in Fig. 4.1. In each case, a significant synchronization peak is evident in the cross-correlogram. In this example, the strength of MU synchronization measured by the synchrony index CIS was 50 - 70% weaker in both hands of the skill-trained subject, and the dominant hand of the untrained subject compared to both hands of the strength-trained subject and the non-dominant hand of the untrained RH subject.

The extent of FDI MU synchronization is summarised for the three subject groups in Fig. 4.2. The strength of MU synchronization (index CIS) in FDI was significantly different in the three subject groups, and the group x hand interaction was significant in the ANOVA (Table 4.1). Skill-trained subjects (0.22 ± 0.02 s^{-1}, 162 MU pairs) exhibited significantly lower MU synchronization than the untrained subjects (0.32 ± 0.02 s^{-1}, 199 MU pairs; Scheffe's F test, $P < 0.05$) and strength-trained subjects (0.44 ± 0.03 s^{-1}, 183 MU pairs; Scheffe's F test, $P < 0.01$). Mean CIS values were also significantly different ($P < 0.01$) for untrained and strength-trained subjects. For all subjects, the mean number of MUs in each hand was 17 (range 7-31). FDI MU synchrony in the dominant hand of the skill-trained group (0.22 ± 0.02 s^{-1}) was significantly different from the dominant ($P < 0.01$) and non-dominant ($P < 0.05$) hands of strength-trained subjects (0.47 ± 0.04 s^{-1} and 0.41 ± 0.05 s^{-1}, respectively) and the non-dominant hand of untrained subjects (0.39 ± 0.03 s^{-1}; $P < 0.05$). FDI MU synchrony in the non-dominant hand of skill-trained individuals (0.22 ± 0.04 s^{-1}) was significantly different from the dominant hand of strength-trained subjects ($P < 0.01$) and the non-dominant hand of untrained subjects (0.39 ± 0.03 s^{-1}; $P < 0.05$). Furthermore, there was a significant difference in FDI MU synchrony in the dominant hands of strength-trained and untrained subjects (0.23 ± 0.03 s^{-1}; $P < 0.01$). To summarise, the strength of FDI MU synchrony in both hands of skill-trained subjects was equivalent to that found in the dominant (skilled) hand of untrained subjects. Strength of FDI MU synchrony in the non-dominant hand of untrained subjects was equivalent to that found in both hands of

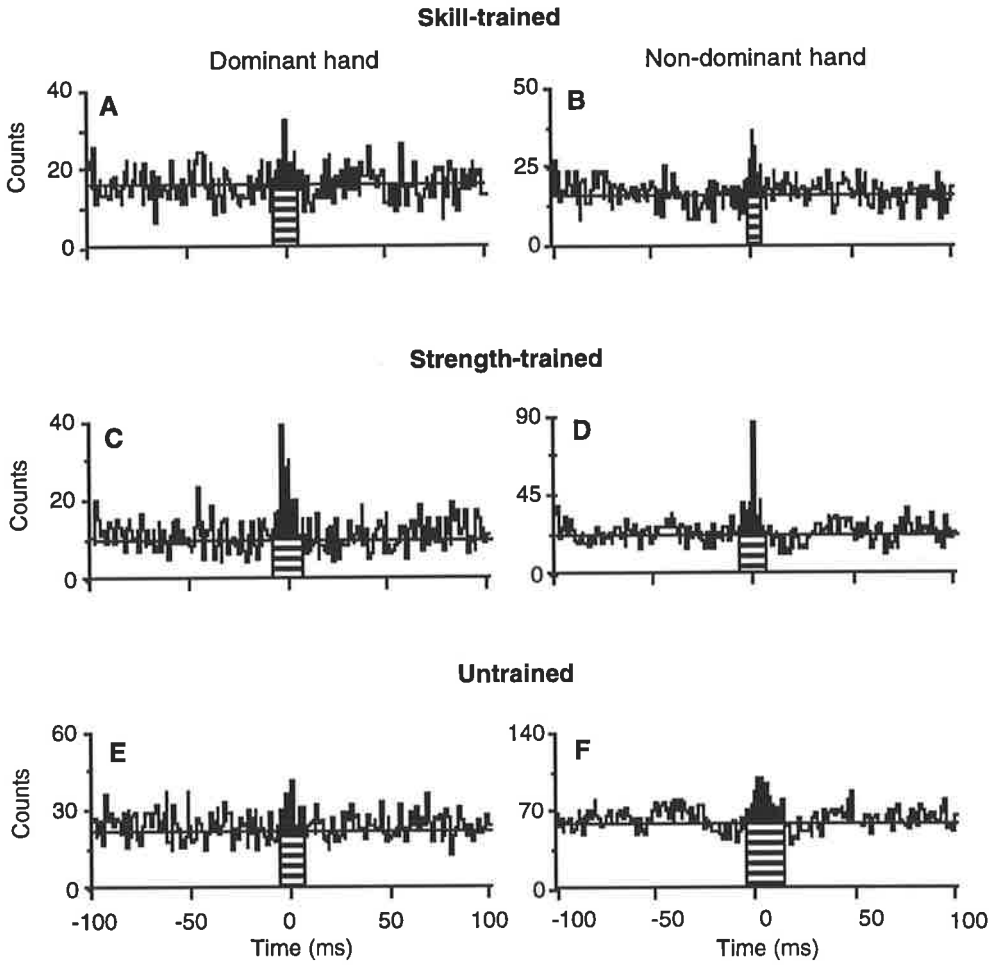

Figure 4.1 Representative examples of motor unit synchronization from the dominant and non-dominant hands of skill-trained, strength-trained and untrained subjects.

A, B, Skill-trained subject. Each graph shows a typical cross-correlogram of the discharge times of two MUs from the dominant (A) and non-dominant (B) hand of one subject. The solid horizontal line represents the mean bin count of the cross-correlogram from bins outside of the peak region. This distinguished between the counts expected due to chance (horizontally hatched area) from the extra synchronous discharges within the peak region (black area). ***C, D,*** Strength-trained subject, arranged as in A, B. ***E,F,*** Untrained RH subject, arranged as in A,B. In this example, the strength of MU synchronization was 50-70% weaker in both hands of the skill-trained subject (CIS, dominant *vs.* non-dominant; 0.28 s^{-1} *vs.* 0.25 s^{-1}) and the dominant hand of the untrained subject (CIS = 0.29 s^{-1}) compared to both hands of the strength-trained subject (CIS, dominant *vs.* non-dominant; 0.75 s^{-1} *vs.* 0.76 s^{-1}) and the non-dominant hand of the untrained subject (CIS = 0.68 s^{-1}).

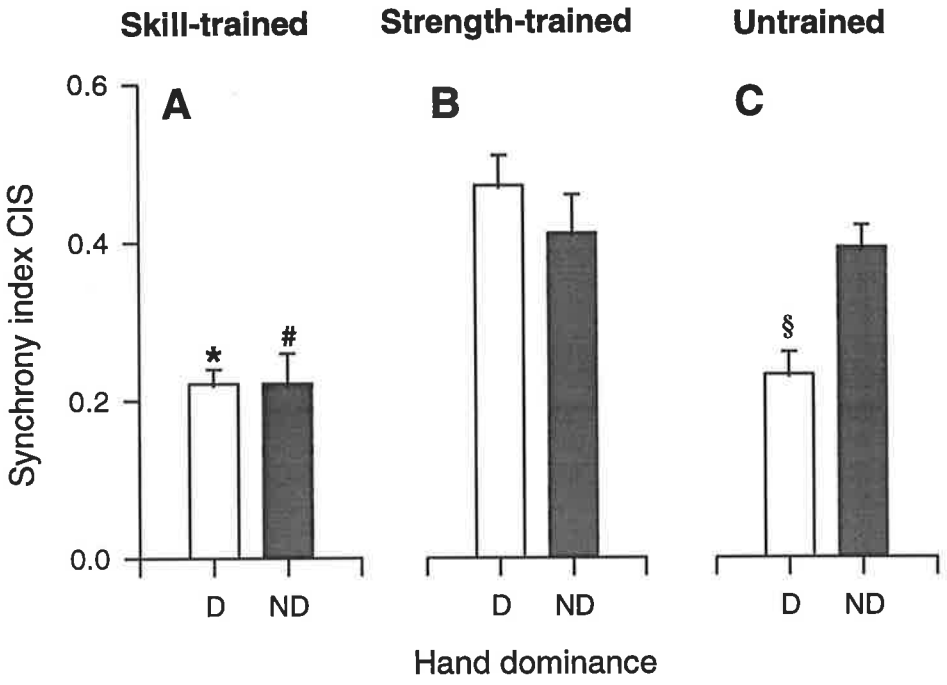

Figure 4.2 Strength of motor unit synchronization in dominant and non-dominant hands of skill-trained, strength-trained and untrained subjects.

Mean (± S.E.) MU synchronization index CIS from cross-correlograms of MU discharge obtained in each hand of ***A***, skill-trained (162 MU pairs), ***B***, strength trained (183 MU pairs) and ***C***, untrained (199 MU pairs) subjects. Dominant hand (D) unfilled bars, non-dominant hand (ND) filled bars. * significant difference (Scheffe's F test) dominant hand skill-trained subjects *vs.* dominant ($P < 0.01$) and non-dominant hands ($P < 0.05$) strength-trained subjects and non-dominant hand ($P < 0.05$) of untrained subjects. # significant difference non-dominant hand of skill-trained subjects *vs.* dominant hand strength-trained subjects ($P < 0\ 01$) and non-dominant hand of untrained subjects ($P < 0.05$). § significant difference dominant hand untrained *vs.* dominant hand strength-trained subjects ($P < 0.01$).

strength-trained subjects.

The width of significant synchronization peaks in the cross-correlation histograms from MU pairs was not uniform for all groups and hands (Table 4.1). Post-hoc tests revealed no significant differences between subject groups (Scheffe's F-test; $P > 0.05$). There was a significant difference in MU synchronization peak width between the dominant and non-dominant hands (19.5 ± 1.2 ms [$n = 45$] *vs.* 15.5 ± 0.6 ms [$n = 90$]; $P < 0.05$) of untrained subjects, which was reported in Chapter 2. There were no significant differences in width of significant synchronous peaks between dominant and non-dominant hands for skill-trained (14.1 ± 0.8 ms [$n = 39$] *vs.* 15.6 ± 0.9 ms [$n = 31$]; $P > 0.05$) or strength-trained (16.4 ± 0.7 ms [$n = 71$] *vs.* 15.3 ± 0.7 ms [$n = 45$]; $P > 0.05$) subjects. The mean synchronous peak width for the dominant hand of untrained subjects was significantly ($P < 0.05$) wider than those from each hand of the other groups, with the exception of the dominant hand of strength-trained subjects.

4.3.2 Common drive and training status

Due to the high degree of discrimination accuracy (virtually 100% of MU discharges correctly identified) required for the reliable assessment of the extent of common fluctuations in mean firing rate (common drive) in pairs of MUs, fewer MU pairs were analysed for common drive than for MU synchronization. The data for this 49 MU pairs (80 MUs) used in the common drive analysis for the three subject groups are summarised in Fig. 4.3A and Table 4.1. The mean common drive coefficient ρ for pairs of FDI MUs was significantly lower in skill-trained subjects (0.30 ± 0.04, $n = 14$) than in strength-trained (0.48 ± 0.03, $n = 21$; Scheffe's F test, $P < 0.001$) and untrained subjects (0.43 ± 0.03, $n = 14$; Scheffe's F test, $P < 0.05$).

In Fig. 4.3B, the MU synchronization data are presented for the 49 MU pairs used for the common drive analysis (i.e. a subset of the data shown in Fig. 4.2). For these MU pairs, the strength of FDI MU synchronization was significantly lower in skill-trained subjects (0.21 ± 0.08 s^{-1}, $n = 14$) than in strength-trained (0.93 ± 0.14 s^{-1}, $n = 21$, $P < 0.01$) and

Figure 4.3 Mean common drive and motor unit synchronization indices for 49 motor unit pairs in skill-trained, strength-trained and untrained subjects.

A, Mean values for common drive cross-correlation coefficient (ρ) for 3 skill-trained (unshaded bars, 14 MU pairs), 4 strength-trained (dark-shaded bars, 21 MU pairs) and 5 untrained (light-shaded bars, 14 MU pairs) subjects. # significant difference (Scheffe's F-test) between skill- and strength-trained subjects ($P < 0.01$) and between skill-trained and untrained subjects ($P < 0.05$). ***B***, Mean synchronization index CIS values from the same 49 MU pairs used to assess the extent of common drive, arranged as in A. * significant difference (Scheffe's F-test) between skill- and strength-trained subjects ($P < 0.001$).

untrained subjects (0.81 ± 0.14 s^{-1}, n = 14, $P < 0.05$).

4. 3. 3 Training status and tremor

Representative examples of force tremor and tremor frequency power spectra for index finger abduction in the dominant hand of a skill-trained, a strength-trained and an untrained subject are shown in Fig. 4.4. These records were obtained during isometric abduction of the index finger with a 3.5 N target force. In this example, the RMS tremor amplitude and peak power in the force frequency spectrum were much higher for the strength-trained subject (54.4 mN and 58.1 mN^2) compared with the skill-trained (17 mN and 32.4 mN^2) and untrained subject (30.4 mN and 48.6 mN^2). The peak frequency in the power spectrum was the same for each hand (6.4 Hz).

The tremor data for the three subject groups are summarised in Fig. 4.5 for target forces of 0.5 N (Fig. 4.5A,C,E) and 3.5 N (Fig. 4.5B,D,F). Tremor RMS amplitude was significantly lower ($P < 0.01$) in skill-trained compared to strength-trained subjects with the 3.5 N target force (Fig. 4.5B), and these differences just failed to reach significance ($P < 0.06$) with the 0.5 N target force (Fig. 4.5A). The peak power in the force frequency spectrum was significantly lower ($P < 0.05$) in skill- compared to strength-trained subjects with the 3.5 N target force (Fig. 4.5D), but the differences failed to reach significance ($P = 0.14$) with the 0.5 N target force (Fig. 4.5C). Differences in tremor amplitude between skill- and strength-trained subjects were not related in a simple manner to peak force capacity of the muscles. Maximal voluntary index finger abduction forces were higher in untrained subjects (44.3 ± 3.1 N) than in skill- (30.0 ± 1.6 N; $P < 0.01$) and strength-trained (32.5 ± 2.7 N; $P < 0.05$) subjects. The peak tremor frequency was similar in the force spectra from all groups for both the 0.5 N and 3.5 N target forces (Fig. 4.5E, F; Table 4.1). When data from all groups were pooled, there was a significant difference in mean peak tremor frequency between dominant (5.7 ± 0.2 Hz) and non-dominant (6.5 ± 0.2 Hz) hands with the 0.5 N target force (Table 4.1), but not with the 3.5 N target force (6.1 ± 0.4 Hz *vs.* 6.4 ± 0.2 Hz).

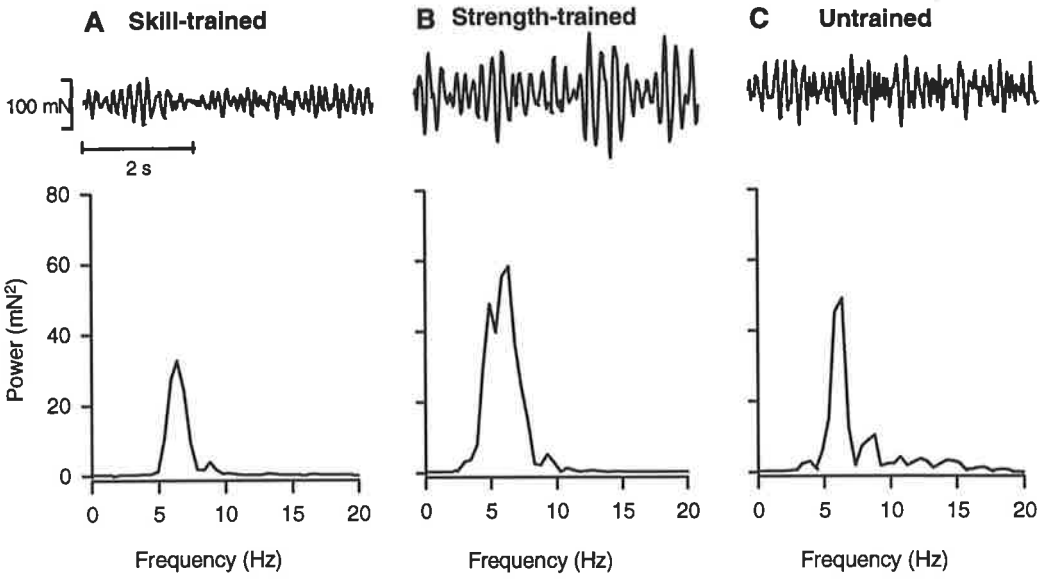

Figure 4.4 Representative examples of force tremor in dominant hands of a skill-trained, strength-trained and untrained subject.

A, Skill-trained subject. Upper trace shows a 5 s epoch of force fluctuations during a 40 s isometric abduction of the index finger with a 3.5 N target force. Force tremor RMS amplitude was 17 mN for this epoch. Lower trace shows the force frequency power spectrum for the same trial. Peak power in the force frequency spectrum was 32.4 mN^2 and tremor peak frequency was 6.4 Hz. ***B***, Strength-trained subject. Index finger isometric abduction with a 3.5 N target force, data arranged as in A. Force tremor RMS amplitude was 54.4 mN, peak power in the force frequency spectrum was 58.1 mN^2, and tremor peak frequency was 6.4 Hz. ***C***, Untrained subject. Index finger isometric abduction with a 3.5 N target force, data arranged as in A. Force tremor RMS amplitude was 30.4 mN, peak power in the force frequency spectrum was 48.6 mN^2, and tremor peak frequency was 6.4 Hz. Tremor RMS amplitude and power at the peak frequency in the force spectrum were lower in the skill-trained subject and higher in the strength-trained subject, than in the untrained subject.

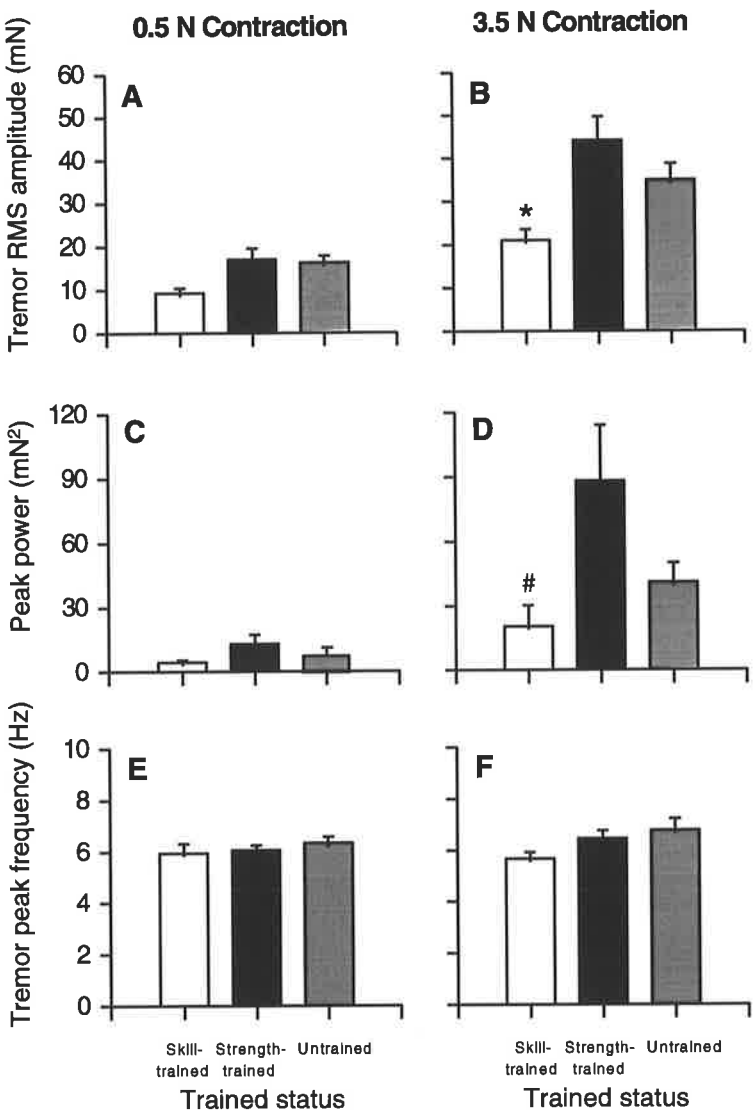

Figure 4.5 Summary of tremor measures obtained at two target force levels in the three subject groups.

Data from both hands of skill-trained (unfilled bars), strength-trained (dark-filled bars) and untrained (light-filled bars) subjects. ***A***, ***B***, mean (± S.E.) tremor RMS amplitude with the 0.5 N (A) and 3.5 N (B) target force. ***C***, ***D***, mean peak power in the force frequency spectrum with the 0.5 N (C) and 3.5 N (D) target force. ***E, F,*** mean tremor peak frequency with the 0.5 N (E) and 3.5 N (F) target force. Significant differences (Scheffe's F test) between skill- and strength-trained subjects are denoted by the symbols * ($P < 0.01$) and # ($P < 0.05$). Tremor RMS amplitude (B) and the peak power in the force frequency spectrum (D) were significantly lower in skill-trained *vs.* strength-trained subjects with the 3.5 N target force. Tremor peak frequency (E, F) did not vary significantly between groups with either target force level.

4. 3. 4 MU discharge properties and tremor

Data from the present study show that training status influenced the extent of correlated MU discharge in FDI, as well as tremor amplitude. MU synchrony, the extent of common drive in MU pairs, tremor RMS amplitude and peak power in the force frequency spectrum all tended to be lower in skill-trained subjects than in strength-trained subjects. In skill- and strength-trained subjects, MU data and tremor measurements were obtained in the same experimental session, and data from these subjects were examined to determine whether differences in MU discharge properties were contributing directly to differences in tremor amplitude.

MU data were pooled to provide a mean value for each FDI muscle of each MU discharge property (mean ISI, CV, CIS, ρ) examined in skill- and strength trained subjects (20 muscles). Linear regression was used to compare the mean MU discharge properties of the FDI muscles with the tremor values obtained when those muscles were activated in the 0.5 N and 3.5 N force-matching tasks.

Linear regression revealed no significant relationships between mean MU ISIs or discharge variability (CV) from FDI muscles and tremor RMS amplitude, peak power in the force frequency spectrum, or tremor peak frequency (r^2 values all < 0.09).

For the comparison of MU synchronization and tremor amplitude, cross-correlograms from 345 MU pairs (mean 17 MU pairs per muscle, range 7 - 31) were used to estimate the overall strength of MU synchrony that was characteristic of each FDI muscle. Linear regression revealed no significant correlation between the extent of MU synchronization in FDI and tremor RMS amplitude during force-matching with either the 0.5 N (Fig. 4.6A; r^2 = 0.001) or 3.5 N (Fig. 4.6B; r^2 = 0.05) target forces. Similarly, there were no significant correlations between FDI MU synchrony and peak power in the force frequency spectrum at the 0.5 N (Fig. 4.6C, r^2 = 0.02) or 3.5 N (Fig. 4.6D, r^2 = 0.07) target forces. No relationship existed between FDI MU synchrony and the peak frequency in the force frequency spectrum (0.5 N, r^2 = 0.002; 3.5 N, r^2 = 0.03).

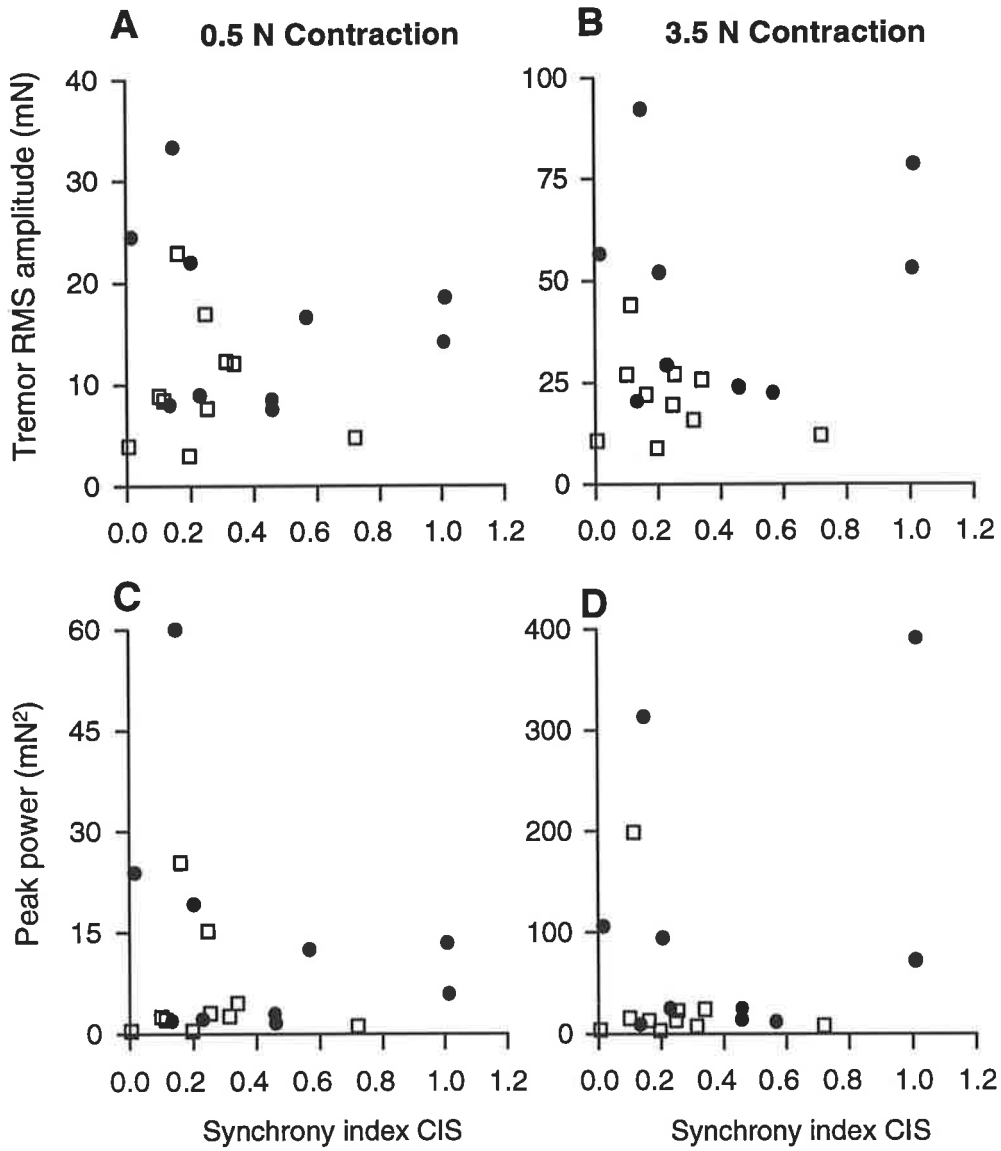

Figure 4.6 Relationship between motor unit synchronization in first dorsal interosseous and force tremor recorded in the same experimental session.

A,B, Data from skill- (unfilled squares) and strength-trained (filled circles) subjects showing the mean MU synchronization index CIS for each FDI muscle plotted against the tremor RMS amplitude during isometric abduction of FDI with 0.5 N (A) and 3.5 N (B) target force levels. ***C,D,*** Data showing the mean MU synchronization index CIS plotted against the peak power during isometric abduction of FDI with 0.5 N (C) and 3.5 N (D) target force levels. Symbols as in A,B. Linear regression revealed no significant correlation between mean MU synchrony in FDI muscles and tremor RMS amplitude or peak power with either target force.

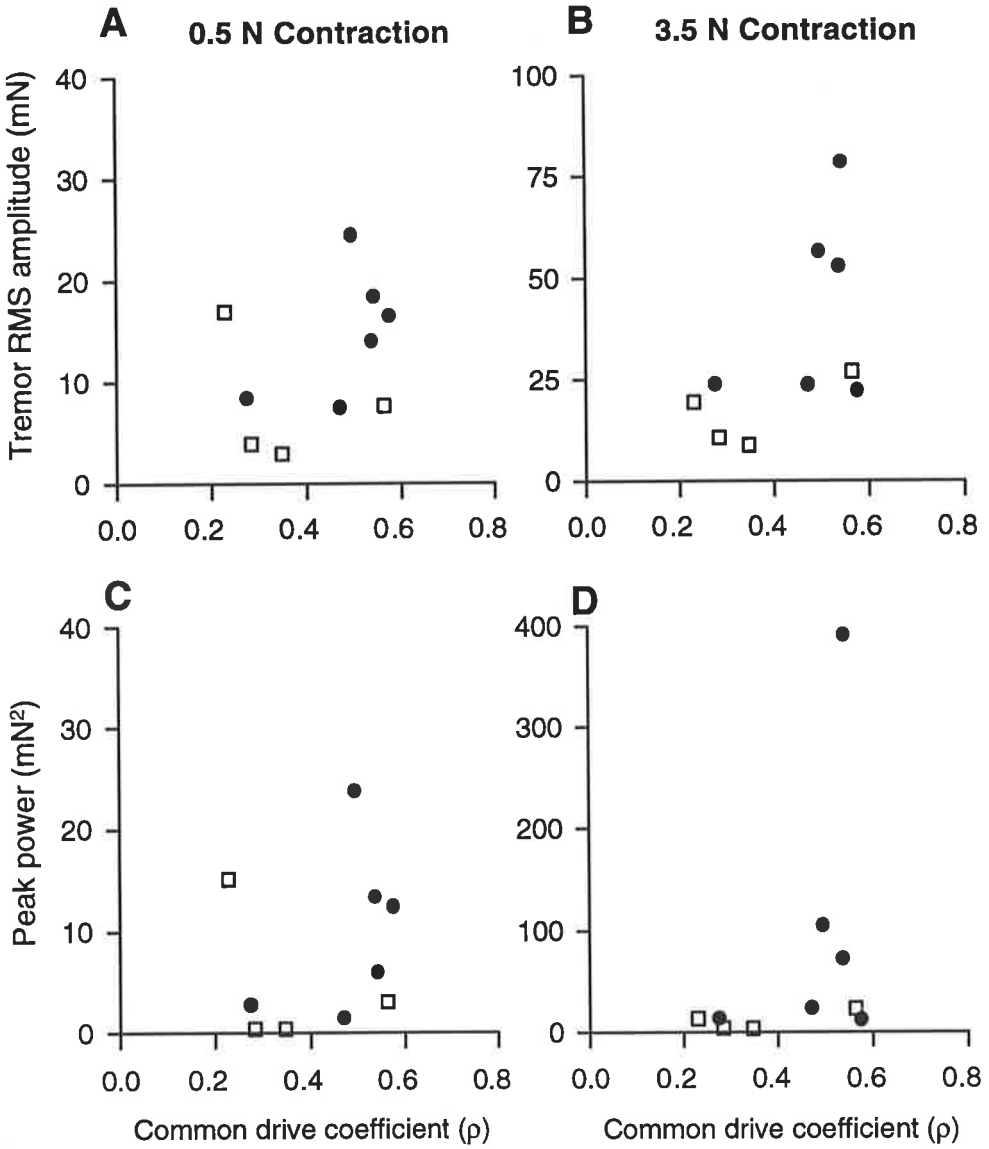

Figure 4.7 Relationship between the extent of common drive in first dorsal interosseous motor unit pairs and force tremor recorded in the same experimental session.

A, ***B***, Data showing the mean common drive coefficient (ρ) for MU pairs in FDI muscles plotted against the tremor RMS amplitude during isometric abduction of FDI at 0.5 N (A) and 3.5 N (B). ***C***, ***D***, Data showing the mean common drive coefficient (ρ) for MU pairs in FDI muscles plotted against the peak power during isometric abduction of FDI at 0.5 N (C) and 3.5 N (D). Symbols as in Fig. 4.6. Linear regression revealed no significant correlation between mean common drive coefficient (ρ) in a muscle and tremor RMS amplitude or peak power with either target force.

Because of the stringent criteria for MU discrimination accuracy for common drive analyses, fewer MU pairs (n = 35, average 3.5 per muscle, range 1 - 6) were used in the estimate of the overall extent of common drive characteristic of each FDI muscle, and data were included from 10 muscles (3 skill- and 3 strength-trained subjects) for comparison with tremor. There were no significant correlations between mean common drive coefficient (ρ) in FDI and tremor RMS amplitude during force-matching with either the 0.5 N (Fig. 4.7A; r^2 = 0.14) or 3.5 N (Fig. 4.7B; r^2 = 0.32) target forces. There were also no significant correlations between mean common drive coefficient (ρ) in FDI and peak power in the force frequency spectrum at the 0.5 N (Fig. 4.7C, r^2 = 0.06) or 3.5 N (Fig. 4.7D, r^2 = 0.16) target forces. No relationship existed between the mean common drive coefficient and the peak tremor frequency in the force frequency spectrum (0.5 N, r^2 = 0.08; 3.5 N, r^2 = 0.19).

4.4 Discussion

The principal finding in this study is that MU discharge properties in FDI and force tremor are not uniform in subject groups distinguished by differing long-term patterns of muscle usage. MU ISIs were slightly shorter on average in the skill-trained subjects than untrained subjects, and MU synchronization and common drive were substantially lower in skill-trained subjects than strength-trained and untrained subjects. Tremor amplitude was lower in skill-trained subjects than strength-trained subjects, while tremor amplitude in untrained subjects was intermediate between the two. Differences in the MU discharge properties examined were not responsible for the differences in tremor amplitude between groups, as analysis at the level of individual muscles revealed that these properties were relatively independent.

4.4.1 Discharge of single MUs and training status

There is evidence from Cracraft & Petajan (1977) which suggests that the firing properties of tibialis anterior MUs can be altered by training. They found that tibialis anterior MUs fired less regularly following a program of high-intensity, short-duration exercise (strength-

training), while more regular MU discharge was the result of a program of low-intensity, long-duration exercise (endurance-training). This finding raises the possibility that different muscle usage patterns may be responsible for the two-fold range in mean discharge variability of FDI MUs in different untrained subjects (Nordstrom *et al.* 1992). In the present study, habitual generalised strength-training (i.e., not specifically involving FDI) over a long period of time did not influence discharge rate and variability of low-threshold single MUs in FDI. Habitual skill-training over an extended period, which was specific to the fingers in the musicians, did not influence discharge variability and had only a modest effect on FDI MU discharge rates, which were 0.5 Hz higher on average in these subjects than untrained subjects. Under the present experimental conditions, the small difference in MU discharge rate may be the result of skill-trained subjects preference to control their MUs at a slightly higher "comfortable" rate. Testing under more standardised conditions are needed before concluding that MU discharge rates are systematically reduced in individuals who consistently perform skilled movements of the digits such as musicians.

4.4.2 MU short-term synchronization and training status

Cross-correlation histograms of MU discharge times revealed narrow peaks of increased discharge probability near the time of firing of the reference MU, characteristic of short-term synchronization. The width of significant synchronous peaks was 4-5 ms wider on average in the dominant hand of untrained subjects, but peak width did not differ significantly between training groups. Broad central peaks (> 40 ms), which are believed to arise from different mechanisms (Kirkwood *et al.* 1982), were extremely rare (0.4%). Eight cross-correlograms (1.5%) had peaks widths greater than 30 ms, and sixty-five (12%) cross-correlograms had peak widths greater than 20 ms.

MU synchrony was significantly weaker in skill-trained subjects than untrained and strength-trained subjects. The strength of FDI MU synchronization in both hands of skill-trained subjects was equivalent to that found in the dominant (skilled) hand of untrained RH subjects, and the overall extent of MU synchrony in these muscles was 41-54% lower than that seen in the non-dominant hand of untrained RH subjects and both hands of strength-

trained subjects (Fig. 4.2). MU short-term synchronization arises from the coincident generation in the motoneurons of EPSPs from common pre-synaptic neurons (Sears & Stagg, 1976; Datta & Stephens, 1990) which slightly increases the probability that the motoneurons will discharge within a few milliseconds of each other. There is now a body of evidence, at least for intrinsic hand muscles, that CM cells from the contralateral motor cortex play a role in producing MU short-term synchronization (see section 1.4.3). The present data suggest that prolonged skilled use of a hand for fine motor tasks such as playing the piano is associated with altered operation of the corticospinal inputs controlling FDI during simple index finger abduction. Reduced MU synchronization in the dominant hand of RH subjects suggests that tasks such as hand writing may also modify the operation of the corticospinal pathway, although this was not revealed in LH subjects (Chapter 2), possibly because they show less lateralisation (smaller difference in hand skill) compared to RH subjects during the performance of skilled tasks (Peters & Servos, 1989; Provins & Magliaro, 1993). Strength-training (not specifically directed at the hand muscles in the present study) was associated with opposite adaptations in corticospinal control of FDI, particularly in the dominant (skilled) hand, based on the finding of higher MU synchrony in FDI of these subjects.

The strength of MU synchronization is influenced by the number of shared branched-axon inputs, their discharge rate, and the size of the unitary EPSPs they produce in the motoneurons (Nordstrom *et al.* 1992). Several possibilities can be advanced to explain reduced MU synchronization in a muscle. First, the *effectiveness* of synchronizing CM projections to FDI motoneurons may be reduced, by a combination of 1) reduced number of CM cells controlling FDI, 2) reduced divergence of monosynaptic CM connexions within the FDI motor pool, and 3) reduced effectiveness of CM unitary EPSPs. The effectiveness of corticospinal inputs to a motor pool can be assessed indirectly in man using TMS. A reduced threshold strength for TMS activation of passive muscle indicates a more effective CM input. The results of three studies using the TMS technique suggest that reduced effectiveness of the CM pathway is unlikely to explain the reduced MU synchrony in subject groups in the present study. Triggs *et al.* (1994) have reported that the threshold for TMS

activation of APB is lower for the hemisphere controlling the dominant hand in both RH and LH subjects. The dominant APB has a larger motor cortical representation than the non-dominant APB (Wassermann *et al.* 1992). Specialised use of the index finger in braille readers is associated with an increased motor cortical representation of muscles in the reading finger (Pascual-Leone *et al.* 1993). While these examples are not definitive, they suggest that skilled use of a hand is more likely to be associated with increased, rather than decreased, effectiveness of corticospinal inputs to hand motoneurons.

The second possible explanation for reduced MU synchronization is that CM cell *activity* is lower during the task when performed by some subject groups. Pyramidal tract neurons projecting to the intrinsic hand muscles are more active during a precision grip than during a power grip (Muir & Lemon, 1983; Lemon *et al.* 1986). Task-related differences have been reported in CM cell excitability (Datta *et al.* 1989; Flament *et al.* 1993) and MU synchrony (Bremner *et al.* 1991c) in man. Training may conceivably alter the pattern of CM cell activity during performance of the simple index finger abduction task, so that it is performed with reduced CM cell involvement when a skilled hand is used. This seems the most likely explanation for the reduced MU synchronization in skill-trained subjects. Evidence exists suggesting that differences in FDI MU short-term synchronization between dominant and non-dominant hands in untrained RH subjects are associated with hemispheric differences in the excitability of corticospinal neurons during the task (Chapter 6). With TMS at passive threshold strength, there was significantly less facilitation of the FDI MEP with voluntary activation when the dominant hand was used for index finger abduction. This suggests that CM cells in the hemisphere controlling the dominant hand were less active during the task than their counterparts in the contralateral hemisphere when the non-dominant hand was used. TES, which activates corticospinal axons, evoked MEPs of comparable size in each hand using the same protocol (see Chapter 6).

Milner-Brown *et al.* (1975) used a method of averaging the surface EMG signal with respect to MU discharge to provide a global estimate of MU synchronization and reported that FDI MU synchrony was stronger in weight-lifters than in untrained subjects. A six-week period

of strength-training of FDI in the non-dominant hand produced an increase in MU synchronization assessed from the surface EMG. The observations of Milner-Brown *et al.* (1975) have been widely cited in the field as examples of neural adaptation to strength training (e.g. Sale, 1987). However, the surface EMG method is a less direct measure of MU synchrony than cross-correlation of MU discharge times, and it is not clear whether the MU synchronization revealed by the two methods are equivalent, or the result of identical physiological processes. Methodological problems, including sensitivity to variations in background EMG levels (signal-to-noise ratio), limit the usefulness of the surface EMG method as an index of MU short-term synchronization (Yue *et al.* 1995). In the present study, strength-trained subjects had higher FDI MU synchronization than untrained subjects, but only in the dominant hand (Fig. 4.2). The association which has been demonstrated between strength-training and higher MU synchrony is in general agreement with Milner-Brown *et al.* (1975), but the differences are less striking than in their study. However, there is evidence in the following chapter (Chapter 5) suggesting that the techniques for detecting correlated MU discharge in the two studies are unlikely to be equivalent.

4.4.3 Common drive and training status

Common drive is the simultaneous modulation of mean firing rates of concurrently active MUs during a voluntary contraction which has a predominant frequency of oscillation in the 1-2 Hz range (De Luca *et al.* 1982b). It reflects a slow modulation of the net excitatory drive to the motoneuron pool. In the present study, the mean common drive coefficient ρ for FDI MU pairs in skill-trained subjects was 60-70% of the values found in strength-trained and untrained subjects (Fig. 4.3). De Luca *et al.* (1982b) has previously reported no significant differences in overall strength of common drive for MU pairs in FDI and deltoid muscles of powerlifters, long-distance swimmers, pianists and control subjects. However, the number of MU pairs examined by De Luca *et al.* (1982b) for between-group comparisons were too small (a total of 12-17 MU pairs from the four subject groups in FDI) to detect anything less than gross differences between groups. In the present comparisons, 49 MU pairs were included from the three subject groups, and statistically significant differences were

demonstrated in the common drive coefficient ρ between the skill-trained subjects and the other two groups. Another difference between the two studies is that the estimate of the common drive coefficient ρ for each MU pair in the present study was an average obtained from four 5-s epochs of steady discharge, which has been found to provide a more reliable estimate of the mean ρ than a single 5-s epoch as used by De Luca *et al.* (1982b) (see Chapter 3).

The last-order neurons responsible for common drive have not been identified. The low-frequency oscillation could be a feature of the descending command signal from supraspinal centres, or arise from activity in segmental interneurons or peripheral afferents. There is some evidence supporting a suprasegmental origin (De Luca & Mambrito, 1987; Kamen *et al.* 1992), but CM cells do not appear to play an important role in the generation of common drive, as regression analysis reveals that the extent of MU synchrony and common drive are only weakly related in MU pairs (Chapter 3). Therefore, the similarity of the pattern of reduced MU synchrony and common drive in skill-trained subjects that is observed in the present study may not be indicative of systematic training-related differences in a single neural control mechanism. While it seems reasonable at present to ascribe differences in MU synchrony to differences in CM cell activity, the origin of reduced common drive in MUs of skill-trained subjects remains unclear. Nevertheless, both measures of correlated MU discharge indicate that certain features of the neural control of the FDI motoneuron pool are different in skill-trained subjects.

4.4.4 Training status, MU discharge and tremor

Tremor RMS amplitude and peak power in the force frequency spectrum were low in skill-trained subjects, intermediate in untrained subjects, and highest in strength-trained subjects. Significant differences were found between skill- and strength-trained subjects for both measures of tremor amplitude with the 3.5 N target force, but not the 0.5 N target (Fig. 4.5). While it has been reported that tremor is enhanced for a period of time following strong muscular contractions (Furness *et al.* 1977), the mechanism is unclear. The CNS plays

some role, because tremor is enhanced in the period following an attempted forceful contraction in which the muscle is prevented from contracting by short-term ischaemic nerve block (Furness *et al.* 1977). Until now, there have been no reports of reduced finger tremor in musicians, who have highly developed finger control.

Mechanisms of tremor production include interaction between firing patterns of MUs (firing rates, variability, synchronization) that are transduced into mechanical events by the muscle; mechanical properties of the extremity; segmental reflex mechanisms (which may reinforce mechanical oscillations); and oscillatory driving of MUs by some CNS mechanism (reviewed by Stein & Lee, 1981). Under conditions of a low force isometric contraction in the present study, the finger was not free to move, so the role of mechanical oscillation of the digit and inputs from segmental reflex mechanisms in the generation of force tremor is probably minor (see Freund & Dietz 1978). In contrast, the unfused twitches of MUs discharging at sub-tetanic rates are a major component of force tremor in the 6-12 Hz range (Allum *et al.* 1978; Christakos, 1982). The relatively large, last-recruited MUs firing at low (least-fused) rates make the greatest contribution to force fluctuations in the active muscle. In human FDI, newly recruited MUs begin firing at between 6-8 Hz (Freund *et al.* 1975) and this may explain why published force frequency spectra for isometric contractions of FDI have the peak power in this frequency band (Stephens & Taylor, 1974; Allum *et al.* 1978; Galganski *et al.* 1993). In the present study, the peak tremor frequency was approximately 6 Hz for all subjects. The small difference (0.5 Hz) in mean MU firing rates in skill-trained and untrained subjects is too small to have a detectable effect on peak tremor frequency (the frequency resolution of power spectral analysis was 0.5 Hz in the present study). Tremor peak frequency was lower in the dominant hand for the 0.5 N contraction but not the 3.5 N contraction. This might reflect differences in MU discharge patterns between hands in the low-force contraction, but at present there are no objective data supporting this suggestion. No differences in tremor peak frequency between hands were noted in Chapter 2, which included LH subjects.

Differences in mean MU discharge rates (altering the relative twitch fusion), variability (Elek

et al. 1991), synchronous discharge (Allum *et al.* 1978; Christakos, 1982), and common modulation of MU discharge rates (Elble & Randall, 1976) may all influence tremor. The influence of these MU discharge properties on force tremor was examined by comparing FDI MU discharge and tremor recordings obtained in a single experimental session. Mean values for each muscle in skill- and strength-trained subjects were subjected to linear regression analysis. These subject groups had the largest difference in tremor amplitude. There were no significant differences in mean MU ISI or CV between skill- and strength-trained subjects, suggesting that these discharge properties were not contributing to tremor differences in the two groups. This conclusion is supported by the linear regression analysis of data from individual muscles, which revealed no significant relationships between MU ISI or CV and tremor RMS amplitude or peak power in the frequency spectrum.

MU synchronization and common drive are two forms of correlated MU discharge which have the potential to influence tremor amplitude, although they are not necessary for tremor generation (Elble & Randall, 1976; Allum *et al.* 1978; Christakos, 1982). Although these two phenomena do not arise from the same mechanism (see Chapter 3), it was found that MU synchronization and common drive were both lower in skill-trained subjects. It is tempting to consider that the more stochastically independent discharge of FDI MUs in skill-trained subjects contributed to the lower tremor amplitude in these subjects compared with strength-trained subjects.

It has been reported that the extent of MU synchrony in FDI muscles contributed only about 6% of the variation in tremor amplitude during index finger abduction (Chapter 2). Data from the untrained RH subjects in the present study, and a group of untrained LH subjects, were used in that study. The conclusion from a previous study (Chapter 2) that the weak MU synchronization displayed by normal subjects in FDI is not an important determinant of finger tremor is in agreement with Logigian *et al.* (1988), but are in some conflict with those of Dietz *et al.* (1976) who found a positive correlation between MU synchrony and tremor amplitude that was significant in gastrocnemius/soleus, but not in FDI. One difference between the previous study and the Dietz *et al.* (1976) study was that the tremor and MU

recordings were obtained in separate sessions (see Chapter 2). To avoid the possibility that sessional variations in MU discharge properties and tremor might obscure a correlation between them when the data were obtained in that way, comparisons between MU synchrony and tremor amplitude in the present study were made from data obtained from the same session (available for skill- and strength-trained subjects only).

The present study confirms the previous finding (Chapter 2) that the strength of MU synchronization in normal FDI muscles is a poor predictor of tremor amplitude. While the skill-trained subjects as a group had lower MU synchrony and tremor than strength-trained subjects, at a single muscle level these variables were not significantly correlated (Fig. 4.6). The influence of MU synchrony on tremor is weak because a) synchronous discharges above chance level are relatively infrequent events in pairs of concurrently active MUs (approximately 0.2 - 0.5 extra synchronous discharges per second), and b) synchronous discharges in different pairs of MUs are not correlated in time (Dengler *et al.* 1984; De Luca *et al.* 1993).

Common drive might be expected to have a stronger influence on force fluctuations than MU synchrony because a) the common drive fluctuations in mean firing rate occur simultaneously throughout the entire motoneuron pool (De Luca *et al.* 1982b), and b) the 1-2 Hz peak amplitude of the fluctuations in mean rate (which have a period of 0.5 - 1 sec) will have a significant effect on force produced by FDI MUs discharging in the 6-12 Hz range where they are in the steep part of the force-frequency relationship and their twitches are unfused (Kirkwood, 1979). A widely distributed 1-2 Hz frequency modulation of MUs discharging with mean rates in the 6-12 Hz range could contribute to tremor in the 6-12 Hz frequency band. In the present study, the extent of common drive of MU mean firing rates in FDI muscles was not significantly correlated with tremor amplitude (Fig. 4.7). For technical reasons (see Methods), this analysis was performed using fewer MU pairs per muscle and ten rather than twenty muscles, which reduces the likelihood of detecting a significant relationship. The linear regression coefficient (r^2) for the relationship between common drive coefficient ρ and tremor RMS amplitude was 0.32 ($P = 0.09$) for the

contraction at the 3.5 N target force (Fig. 4.7B). This was the strongest correlation between any MU discharge variable and tremor, but failed to reach significance.

The differences in neural control of FDI in skill-trained subjects that are reflected in reduced MU synchronization and common drive are not responsible for the lower tremor amplitude in these subjects. One remaining possibility is a difference in the mechanical twitch properties of low-threshold FDI MUs discharging in the 6-12 Hz range. STA of twitch forces (Milner-Brown *et al.* 1973a) might provide some evidence on this point, but interpretation is complicated by the different amounts of MU synchrony in the subject groups, which will introduce systematic errors in MU twitch estimation using STA. With regard to the mechanical state of the muscle, the differences in tremor amplitude between skill- and strength-trained subjects were not related to differing maximal force capacity of FDI muscles, as this was not significantly different in these subject groups. It was surprising that MVC force was greatest for untrained subjects compared to strength-trained subjects, however the strength-trained subjects were not involved in any activity which specifically trained the FDI muscle, but a much more generalised training of the upper limbs. The untrained subjects included a full spectrum of MVC forces from individuals not trained in any particular task, and included some individuals with MVCs that were very large. Perhaps in these subjects a tighter control on restricting MVC force to only the FDI muscle may have prevented this unexpected result.

In summary, FDI MUs in skill-trained subjects and the dominant (skilled) hand of untrained RH subjects displayed weaker MU synchronization than FDI MUs in strength-trained subjects and the non-dominant hand of untrained RH subjects. Common drive of firing rates was weaker in skill-trained subjects than strength-trained and untrained subjects. These differences are indicative of altered neural control of FDI motoneurons in these hands. In the case of weaker MU short-term synchronization, reduced activity of the corticospinal pathway during task performance seems the most likely explanation. Tremor amplitude was lower in skill-trained subjects than strength-trained subjects, but this was not a direct result of the more independent discharge of their FDI MUs.

CHAPTER 5

THE SURFACE ELECTROMYOGRAPHY TECHNIQUE IS NOT AN ACCURATE ESTIMATE OF MOTOR UNIT SYNCHRONIZATION

5.1 Introduction

During a voluntary isometric contraction, there is an increased tendency for MUs to discharge together more often than purely by chance. This is evident from the cross-correlation of individual discharge times of two MUs, in which the times of firing of the reference spike, defined as time zero, are correlated with those of the other spike train, termed the event MU. If a tendency towards synchronous MU discharge exists, there will be a narrow peak of increased discharge probability in the cross-correlogram around the time of firing of the reference MU. The appearance of this narrow central peak is particularly prominent in distal hand muscles (Datta & Stephens, 1990; De Luca *et al.* 1993), and branched-axon inputs to motoneurons from corticospinal neurons are believed to be important in its generation (Datta *et al.* 1991; Farmer *et al.* 1993b). Results from recent MU cross-correlation experiments suggest that MU synchronization may be altered under various behavioural conditions (Adams *et al.* 1989; Bremner *et al.* 1991c). These include modifications involved with constant preferential use of the hand (Chapter 2), and systematic differences in MU synchronization in individuals who have performed many years of skill- or strength-related training (Chapter 4). These results indicate that the operation of the corticospinal pathway may be altered under these circumstances.

One drawback of the cross-correlation technique is that many MUs are required to obtain a reliable estimate of MU synchrony because large variations in the strength of MU

synchronization exist in different MU pairs in the same muscle (Bremner *et al.* 1991a; Nordstrom *et al.* 1992). It is not always possible to record from a large number of MU pairs in a single experiment. Also, MU short-term synchrony is very weak, and requires a large number of MU discharges to be detected reliably, and therefore trials of long duration need to be recorded. Although estimates of MU synchronization from cross-correlation reveal important information concerning fine motor control in humans (e.g., see Farmer *et al.* 1993b), these complications constrain its usefulness.

In an attempt to provide an estimate of MU synchronization within a population of MUs, Milner-Brown *et al.* (1973a) used a method of averaging the surface EMG signal with respect to MU discharge. This method consists of comparing the simultaneously recorded unrectified and full-wave rectified surface EMG which has been triggered by the discharge of a reference MU in the muscle. The unrectified surface EMG average essentially represents the contribution of only the reference MU to the surface EMG, because the contribution of the positive and negative waveform components from other MUs not synchronized to the reference MU average to zero. The rectified surface EMG provides a measure of the total electrical activity in the muscle at the time of reference MU discharge, which includes the waveform of the reference unit after rectification, an average EMG level (background) due to independent firing of other MUs, an artifact associated with signal rectification (due to a partial summation of the rectified waveform and the background activity; (Milner-Brown *et al.* 1973a; see also Yue *et al.* 1995)), and the contribution of other MUs that are synchronized to the reference MU. The difference between the two rectified and unrectified averages (above background discharge) therefore provides an index for a global estimate of MU synchronization. However, in the original method, Milner-Brown *et al.* (1973a) recognised that the rectification artifact and the amount of MU synchronization varied with the signal-to-noise ratio, and they used a theoretical model to calculate this contribution. Despite later indications that the surface EMG method was a sensitive index (Roscoe *et al.* 1985), they chose to simplify the calculation by assuming that the rectification artifact was fixed. Using the simplified method, Milner-Brown *et al.* (1975) reported that FDI MU synchrony was stronger in weight-lifters than in untrained subjects. Also, a six-week period

of strength-training of the FDI muscle produced an increase in MU synchronization which was attributed to strengthening of transcortical reflex pathways. These observations have been widely accepted as a training-related neural adaptation, and have been implicated in the increases in strength following training (e.g. Sale, 1987). However, it has recently been reported that the contribution of the rectification artifact to the amount of synchronization varies non-linearly with the signal-to-noise ratio (Yue *et al.* 1995), which brings into question the reliability of the simplified surface EMG method as an estimate of MU synchronization.

The simplified surface EMG method is a less direct measure of MU synchrony than cross-correlation of MU discharge times, and it is not clear whether the estimate of MU synchronization revealed by the two methods are equivalent. Because of the sensitivity of the surface index to the signal-to-noise ratio, it is unknown whether the simplified surface EMG method gives a reliable, overall impression of MU short-term synchronization in a muscle which is equivalent to that obtained with cross-correlation of a large sample of MU pairs. It is also unclear whether the two methods are measuring identical physiological processes; for example, whether MUs that display short-term synchronization (in that the MU discharges are closely time-locked to the firing of each other, such as in FDI) are accurately detected with this method. In an earlier study using the cross-correlation technique (Chapter 4), strength-trained subjects had higher FDI MU synchronization than untrained subjects, but only in the dominant hand. This affinity between strength-training and higher MU synchrony is in general agreement with Milner-Brown *et al.* (1975), but the differences were less impressive than in their study. For these reasons, I undertook a direct comparison of the overall level of MU synchronization in a muscle by the two methods. Recording from a large number of MUs per muscle ensures a reliable estimate of MU synchronization using cross-correlation of MU pairs. In the same muscle, a large number of reference MUs averaged to the surface EMG will provide an overall estimate of MU synchronization using the surface EMG technique. The MU recordings from skill-trained, strength-trained and untrained subjects in the previous studies (Chapters 2 and 4) were used, as it is reasonably expected that they will provide a large range in the strength of MU

synchronization for different muscles. This also provided the opportunity to verify the findings of Milner-Brown *et al.* (1975) using the surface EMG method in strength-trained subjects.

5.1 Methods

MU activity was recorded from FDI muscle in sixteen healthy adults (ages 18-47 years). Five of these subjects regularly lifted weights (denoted strength-trained subjects), five were highly skilled musicians (skill-trained subjects) and six subjects reported no special use of their hands (untrained subjects). Further details of these subjects can be obtained in Chapter 4. All subjects volunteered to participate in the study and gave informed consent to the procedures, which were approved by the Committee for the Ethics of Human Experimentation at the University of Adelaide. Hand dominance was assessed by the Edinburgh Handedness Inventory (Appendix A) which resulted in LQ values between +1 (entirely RH) and -1 (entirely LH). Fifteen subjects were RH (mean LQ 0.9, range 0.5 - 1.0), and one skill-trained subject was LH (LQ = -1.0).

5.2.1 Experimental arrangement

The experimental arrangement and protocol for recording the surface EMG and MU discharge properties have been described previously (Chapters 2, 3 and 4). Briefly, subjects attended the laboratory on two or more separate occasions, where surface EMG and MU activity were recorded from one hand on each occasion. The subjects' right or left arm and hand were secured in a manipulandum, where the force of abduction was measured by a load cell which was aligned with the distal interphalangeal joint of the index finger (see Plate 2.1). The surface EMG of the left and right FDI was recorded with bipolar Ag-AgCl electrodes placed 2-3 cm apart. MU activity was recorded simultaneously with two separate fine-wire electrodes (1-2 cm interelectrode distance) which were inserted percutaneously into the FDI with a 25-gauge disposable needle. Myoelectric signals were amplified (1000x), filtered (bandwidth 2 Hz-10 kHz) and recorded on FM tape (Vetter model 400D, Rebersburg, PA,

USA, 22 kHz/ch) for off-line analysis. The DC force signal was filtered (0 - 50 Hz) and digitised (1 kHz) on-line on a Macintosh computer.

5.2.2 Protocol

The experimental protocol was identical to that described in Chapters 2, 3 and 4.

5.2.3 Analysis

5.2.3.1 MU discrimination

All analyses were performed off-line from the taped records. Single MUs from each intramuscular electrode were discriminated according to the method described in previous chapters (2, 3 and 4). Action potentials belonging to a particular MU were identified on the basis of waveform shape, and great care was taken to confirm the identity of units discriminated during different trials. ISIs of identified MUs were measured (± 250 μs resolution) using an in-built function of the SPS 8701 and stored on computer. ISI records were scrutinised for every trial and each discriminated MU to assess discrimination accuracy. ISI histograms were constructed from the discharge times of each MU. ISI files with >5% discrimination error (usually missed spikes due to superimpositions) were excluded from all analyses.

5.2.3.2 Spike triggered averaging and MU synchronization

For a subset of MUs from the previous study (Chapter 4), TTL pulses corresponding to the time of discharge of a single MU discriminated with the SPS 8701 were sent to a second computer with the corresponding surface EMG (2 kHz sampling rate). The single MU discharge times were used as the reference location (t = 0 ms) for STA of the surface EMG. STA of the digitally full-wave rectified and unrectified EMG was performed with a custom designed computer program written in a graphical programming language (Labview). Each STA had a duration of ± 85 ms from the time of discharge of the reference MU, and was based on 150 reference MU discharges.

A comparison of the area of the unrectified and rectified EMG averages was used to provide an estimate of the strength of MU synchronization within the MU population. This method has previously been described by Milner-Brown *et al.* (1973a; 1975) and is illustrated for one MU in Fig. 5.1. Briefly, STA of the unrectified (Fig. 5.1A) and full-wave rectified (Fig. 5.1C) surface EMG was obtained for each reference MU. The unrectified (with negative phases inverted; Fig. 5.1B) and rectified EMG averages were then superimposed (Fig. 5.1D) and the boundaries for the area of synchronous activity were identified (dashed vertical lines, Fig. 5.1D). This consisted of detecting the first location either side of the central peak, starting at the point of MU discharge (arrow, Fig 5.1D), where the rectified EMG level was equal to the mean EMG level due to the asynchronous firing of other MUs (i.e. background EMG level; dashed horizontal lines, Fig. 5.1C,D). From within the peak region, the area due to the synchronous firing of other MUs was established (black area, Fig. 5.1D). This area represented the area in the rectified EMG trace which was above the baseline activity (black area, Fig. 5.1C), and above the voltage levels which occurred in the unrectified EMG trace (hatched area, Fig. 5.1D). The strength of MU synchronization was determined by computing the ratio of the synchronous area (black area, Fig. 5.1D) to the area of the unrectified EMG within the peak region (dotted and hatched area; Fig. 5.1D).

5.2.3.3 Cross-correlation and MU synchronization

MU synchronization was also assessed using cross-correlation of MU discharge times (Nordstrom *et al.* 1992). This process was described in detail in Chapter 2. The strength of MU synchronization is shown for two MUs using the cross-correlation and surface EMG techniques in Fig. 5.2. The two MUs which form the basis of the cross-correlogram in Fig. 5.2A have each been used as the reference MU for the measure of MU synchronization from STA of the surface EMG in Figs. 5.2B,C. Very different surface EMG synchronization ratios were obtained with the two reference MUs, largely because of the smaller contribution of the reference MU in Fig. 5.2C to the surface average.

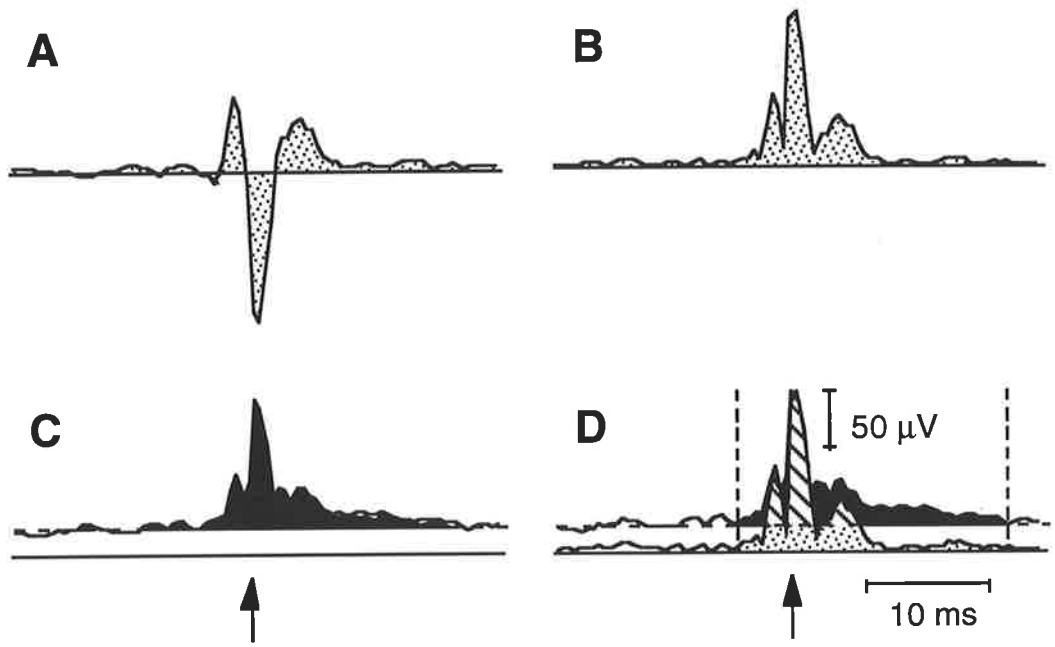

Figure 5.1 Procedure for the estimation of motor unit synchronization from the surface electromyogram.

A, STA of the unrectified surface EMG. The solid horizontal line represents the zero voltage level. ***B***, the unrectified EMG average in A with the negative waveform components inverted. ***C***, STA of the rectified surface EMG. The dashed horizontal line represents the mean background EMG level, which results from the discharge of other, non-synchronized MUs. ***D***, The superimposed waveforms of B and C. The width of the peak (21 ms) is designated by the vertical dashed lines. The area due to the synchronous firing of other MUs (black area) is the area above baseline of the rectified EMG average (black area in C) in excess of the area above baseline due to the unrectified EMG average (hatched area in D). The extent of MU synchronization is calculated from the ratio of the synchronized area (black area in D) to the total area of the unrectified EMG average within the peak region (dotted and hatched area in D). The surface EMG synchrony ratio for this MU is 0.49. The surface EMG averages were based on 150 reference MU discharges. The arrow indicates the time of discharge of the reference MU.

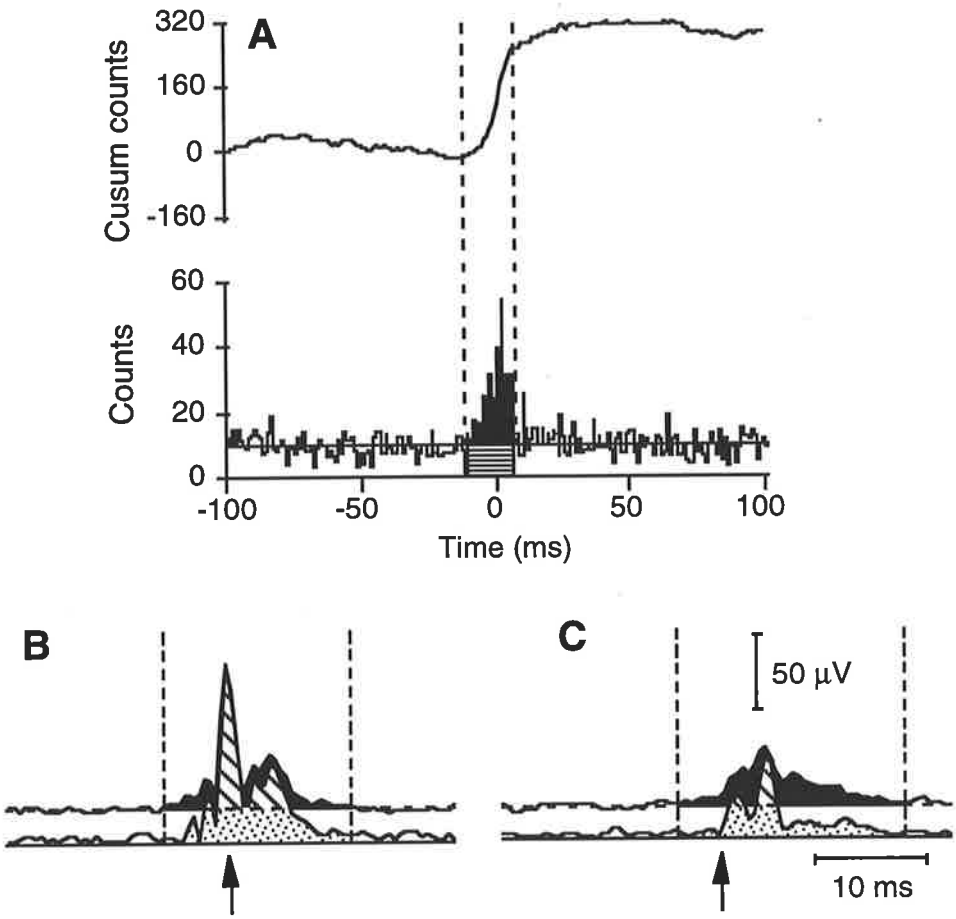

Figure 5.2 Estimation of the strength of MU synchronization from the cross-correlogram and the corresponding surface electromyogram average. *A*, estimation of MU synchrony using the cross-correlation histogram of MU discharge. Lower trace is the cross-correlogram of the discharge times of two concurrently active MUs in FDI. The mean bin count of off-peak bins was 9.7 (horizontal line). This value served to distinguish between the counts expected due to chance (horizontally hatched area) from those counts in excess of chance (black area) in the peak region. The position and duration of the synchronous peak was judged visually from the cumulative sum (CUSUM, upper trace). In this example, the width of the peak (vertical dashed lines) was 19 ms centred at t = -2 ms. The synchronization index CIS for this MU pair was 1.21 extra counts s^{-1}. ***B*** and ***C***, estimation of MU synchrony using the surface EMG spike-triggered averaging method (n = 150) for the two MUs in A. Data arranged as in Fig. 1D. B, The surface EMG synchronization ratio for this MU is 0.31 with a peak width of 19 ms. The arrow indicates the time of discharge of the reference MU. C, data from the second concurrently active MU in A. This MU was used as the reference MU in the cross-correlogram (A). Surface EMG synchronization ratio for this MU was 1.03 with a peak width of 24 ms.

5. 2. 4 Statistical analysis

Data are presented as mean ± S.E. unless otherwise stated. A two-way ANOVA was employed for comparisons of the strength of MU synchrony from the two methods between groups (skill, strength and untrained) and hand (dominant *vs.* non-dominant). Significant effects for group and hand were analysed further with a one-way ANOVA and Scheffe's F test. Linear regression was used to assess the relationship between the strength of synchronization as measured by the synchronization index CIS and the surface EMG ratio. Significance was reported for $P < 0.05$.

5.3 Results

5. 3. 1 Handedness and strength of MU synchronization

The extent of MU synchrony using the STA of the surface EMG was assessed in 189 MUs from 16 subjects (5 skill-trained, 5 strength-trained and 6 untrained subjects). A total of 28 different FDI muscles were analysed from the 16 subjects, as data were excluded from all analyses in the dominant hand of 2 individuals (1 strength-trained, 1 untrained) and the non-dominant hand of 2 individuals (1 skill-trained, 1 untrained) due to a weak surface EMG signal. In relation to hand dominance, the strength of synchronization using the surface EMG synchronization ratio is shown in Table 5.1. This shows the mean surface EMG synchronization ratio for the total number of reference MUs examined. For pooled data, there was no significant difference in the strength of synchronization between dominant and non-dominant hands. The only significant differences were for the dominant hand of skill-trained subjects (0.7 ± 0.07, $n = 29$) and the non-dominant hand of strength-trained subjects (0.69 ± 0.05, $n = 29$) compared to the dominant hand of untrained subjects (0.38 ± 0.05, $n = 27$; $P < 0.05$).

Table 5.1. Strength of synchronization of FDI MUs in dominant and non-dominant hands using the surface EMG technique.

	Surface EMG synchronization ratio	
	Dominant hand	*Non-dominant hand*
Skill-trained	0.70 ± 0.07 (29)	0.54 ± 0.06 (25)
Strength-trained	0.48 ± 0.06 (29)	0.69 ± 0.05 (29)
Untrained	0.38 ± 0.05* (27)	0.59 ± 0.05 (50)
All subjects	0.53 ± 0.04 (85)	0.61 ± 0.03 (104)

Values are mean ± S.E. (number of reference MUs). * significant difference ($P < 0.05$) compared to the dominant hand of skill-trained subjects and the non-dominant hand of strength-trained subjects.

MU synchronization measured from cross-correlation was assessed in pairs of MUs in the same hands used for the surface EMG ratio. A total of 498 MU pairs from the previous study (Chapter 4) were used for this analysis. In these MU pairs, cross-correlation revealed no difference in the strength of MU synchronization between dominant and non dominant hands for pooled data (Table 5.2). The findings of the strength of MU synchronization from cross-correlation in the present study were all similar to those using all available MU pairs as presented in Chapter 4. They indicate that the subset of MU pairs used for the present analyses were representative of the total sample.

Table 5.2. Strength of synchronization of FDI MU pairs in dominant and non-dominant hands using the cross-correlation technique.

	Synchronization index (CIS)	
	Dominant hand	*Non-dominant hand*
Skill-trained	0.22 ± 0.02* (80)	0.21 ± 0.04† (73)
Strength-trained	0.45 ± 0.05 (91)	0.40 ± 0.05 (77)
Untrained	0.25 ± 0.04§ (80)	0.42 ± 0.03 (97)
All subjects	0.31 ± 0.02 (251)	0.35 ± 0.02 (247)

Values are mean ± S.E. (n). * significant difference compared to the dominant hand of strength-trained subjects ($P < 0.01$) and the non-dominant hand of untrained subjects ($P < 0.05$). † significant difference compared to the non-dominant hand of strength-trained subjects ($P < 0.01$) and the non-dominant hand of untrained subjects ($P < 0.05$). § significant difference compared to the dominant hand of strength-trained subjects ($P < 0.05$).

5. 3. 2 Handedness and width of the central synchronous peak

The surface EMG synchrony peak widths were not significantly different between dominant and non-dominant hands for all subjects, or in the individual groups. Similarly, no significant difference was found in the width of the central cross-correlogram peak in dominant and non-dominant hands. Again, similar findings for cross-correlation were obtained from the total pool of MUs examined in Chapter 4.

5. 3. 3 Training and strength of MU synchronization

The mean strength of MU synchronization measured from the surface EMG in 5 skill-trained (54 reference MUs), 5 strength-trained (58 reference MUs) and 6 untrained (77 reference MUs) subjects is shown in Fig. 5.3A. Although significance was detected between the trained groups for the surface EMG ratio (two-way ANOVA; $F[2, 183]=3.4$; $P < 0.05$), post-hoc analysis revealed no significant difference between skill-trained (0.63 ± 0.05),

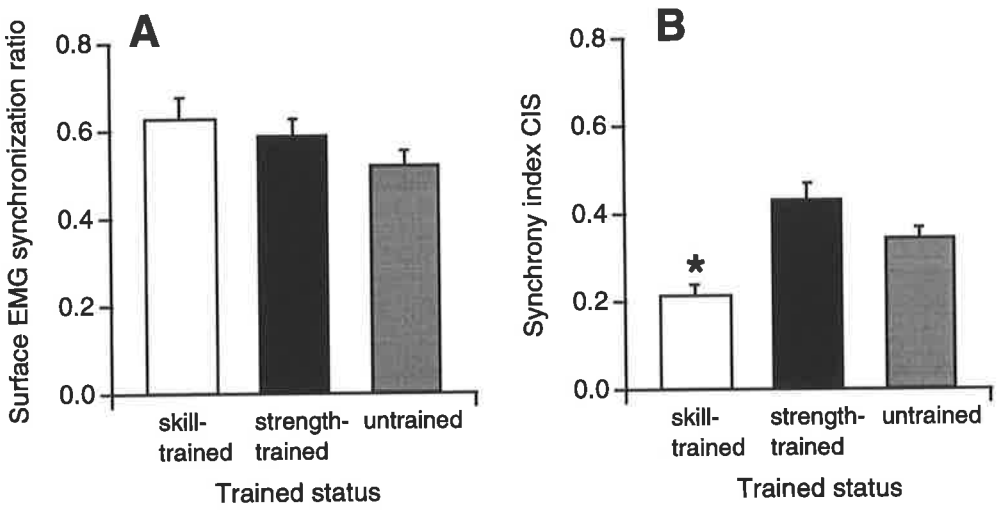

Figure 5.3 Mean strength of motor unit synchronization measured from the surface electromyogram and cross-correlation methods in skill-trained, strength-trained and untrained subjects.

A, Mean (± S.E.) values for the surface EMG synchronization ratio in 5 skill-trained (unshaded bars, 54 MUs), 5 strength-trained (dark-shaded bars, 58 MUs) and 6 untrained (light-shaded bars, 77 MUs) subjects. ***B***, Mean synchronization index CIS values from the same muscles used for the surface EMG synchronization ratios in 5 skill-trained (153 MU pairs), 5 strength-trained (169 MU pairs) and 6 untrained (176 MU pairs) subjects, arranged as in A. * significantly different (Scheffe's F-test) from untrained ($P < 0.01$) and strength-trained ($P < 0.001$) subjects.

strength-trained (0.59 ± 0.04) and untrained (0.52 ± 0.04) subjects.

Fig. 5.3B shows the strength of MU synchronization measured from cross-correlation in the same 16 subjects (skill-trained, 153 MU pairs; strength-trained, 169 MU pairs; untrained, 176 MU pairs) from the previous study (Chapter 4). The strength of MU synchronization measured from cross-correlation (Fig 5.3B) was lower in skill-trained (0.21 ± 0.02 s^{-1}) compared to untrained (0.34 ± 0.02 s^{-1}, $P < 0.01$) and strength-trained (0.43 ± 0.04 s^{-1}, $P < 0.001$) subjects. This relationship between the strength of MU synchronization from cross-correlation in the trained groups was observed in Chapter 4.

5. 3. 4 Training and width of the central synchronous peak

The width of the central synchronous peak in the rectified surface EMG was different in the training groups (Fig. 5.4A; two-way ANOVA; $F[2, 183]=3.4$; $P < 0.05$). Skill-trained subjects had significantly narrower peak widths (15.6 ± 0.5 ms) than strength-trained (18.0 ± 0.8 ms, $P < 0.05$) subjects. The width of the peak in the rectified EMG in the untrained subjects (17.2 ± 0.6 ms) was intermediate between skill- and strength-trained subjects, but was not different from any group.

Training-related differences were also found in the width of the synchronous peak measured from the cross-correlogram of MU discharge (Fig. 5.4B; two-way ANOVA, $F[2, 285] = 6.1$, $P < 0.01$). From a total of 291 significant synchronous peaks, the peak width was significantly different in skill-trained (14.5 ± 0.6 ms, $n = 63$) compared to untrained (16.9 ± 0.6 ms, $n = 123$; $P < 0.05$) subjects. The peak width for the strength-trained subjects (15.6 ± 0.5 ms, $n = 105$) was intermediate between skill-trained and untrained subjects, but was not significantly different from any group.

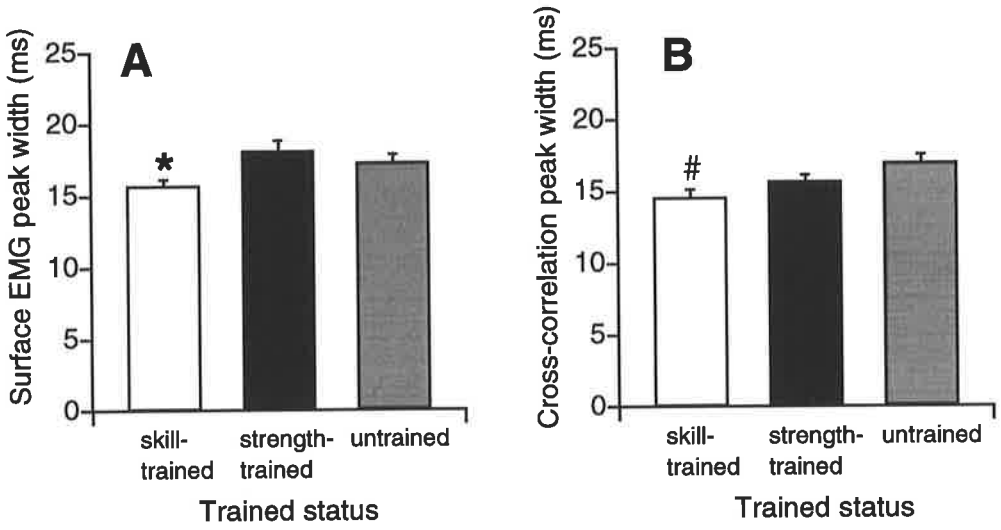

Figure 5.4 Mean width of the central synchronous peak measured from the surface electromyogram and cross-correlation methods in skill-trained, strength-trained and untrained subjects.

A, Mean values for the width of the central peak from the surface EMG in 5 skill-trained (unshaded bars, 54 MUs), 5 strength-trained (dark-shaded bars, 58 MUs) and 6 untrained (light-shaded bars, 77 MUs) subjects. ***B***, Mean width of the central synchronous peak measured from the cross-correlogram in the same 5 skill-trained (63 MU pairs), 5 strength-trained (105 MU pairs) and 6 untrained subjects (123 MU pairs), arranged as in A. * significantly different (Scheffe's F-test) from strength-trained ($P < 0.05$) subjects. # significantly different from untrained subjects ($P < 0.01$).

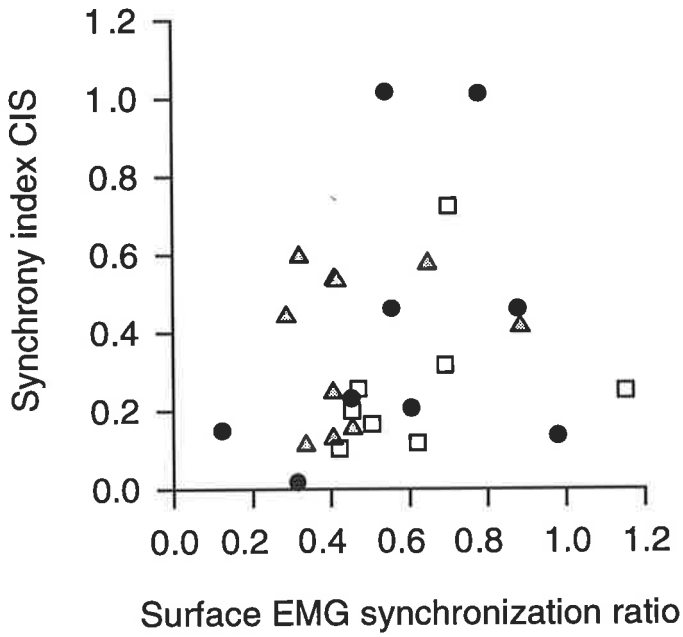

Figure 5.5 Relationship between the estimates of the strength of motor unit synchronization obtained using the surface electromyogram (surface EMG synchronization ratio) and the cross-correlogram (synchrony index CIS).

Data from all subjects showing the mean surface EMG synchronization ratio for each FDI muscle (mean 7 reference MUs per muscle, range 2-15) plotted against the mean MU synchronization index CIS (mean 18 MU pairs per muscle, range 7 - 30). Linear regression revealed no significant correlation between these two estimates of MU synchrony (r^2 = 0.04). Data from the skill-trained (r^2 = 0.08; unfilled squares), strength-trained (r^2 = 0.09, dark-filled circles) and untrained subjects (r^2 = 0.03; light-filled triangles) also failed to reveal any significant correlation between the two synchrony estimates.

5.3.5 Surface EMG and cross-correlation measures of MU synchronization

Mean MU synchronization estimated from cross-correlation and surface EMG techniques were obtained for a total of 28 different FDI muscles. In these muscles, the mean strength of MU synchronization using the surface EMG method varied over a ten-fold range (range 0.12 - 1.15), with an average of 7 (range 2 - 15) reference MUs per muscle used to calculate the mean surface EMG synchronization ratio. The mean strength of MU synchronization (CIS) using cross-correlation of MU discharge varied over a two hundred-fold range (range 0.005 - 1.03 extra counts s^{-1}), with an average of 18 (range 7 - 30) MU pairs per muscle used to calculate the mean synchronization index CIS. The number of MUs sampled per muscle should have ensured a reliable global estimate of MU synchronization with the two methods. These results indicate that the mean strength of MU synchronization calculated with both techniques varied over a large range in different subjects.

For the 28 muscles, linear regression revealed no significant relationship between the two measures of MU synchronization (r^2 = 0.04, Fig. 5.5). Pooled data separated for hand dominance and training groups also failed to provide any significant correlations.

There was no significant correlation between the width of synchronous peaks in a muscle obtained by the two methods (r^2 = 0.05, n = 28, Fig. 5.6). The scatter of points below the line of identity in Fig. 5.6 indicates a tendency for the width of the central synchronous peak to be broader with the surface EMG method.

5.4 Discussion

5.4.1 Relationship between the strength of MU synchronization using the surface EMG and cross-correlation techniques

Cross-correlation of the discharge times of two MUs is a reliable estimate of the overall extent of MU synchronization in a muscle provided that a large number of MUs are sampled from each experiment and long duration trials are used to minimise estimation variability.

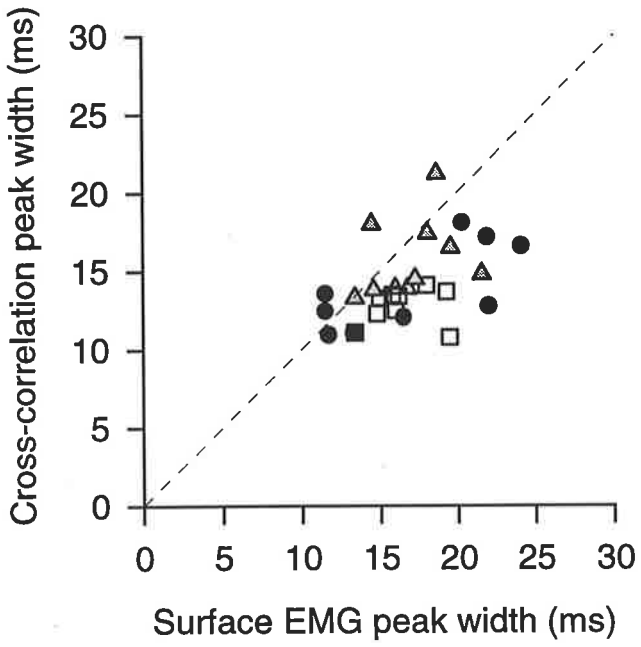

Figure 5.6 Relationship between the width of the central synchronous peak measured from the surface electromyogram and the cross-correlogram.

Data from all subjects showing the mean width of the central synchronous peak in the FDI surface EMG (total 189 MUs) plotted against the mean width of the synchronous peak in the cross-correlogram (total 291 MU pairs) for 28 muscles. The dashed line represents the line of identity. Linear regression revealed no significant correlation between these two estimates of the duration of MU synchrony ($r^2 = 0.05$). Data from the skill-trained ($r^2 = 0.02$; unfilled squares), strength-trained ($r^2 = 0.28$, dark-filled circles) and untrained subjects ($r^2 = 0.02$; light-filled triangles) also failed to reveal any significant correlation between the synchrony measures.

The former condition is necessary because the extent of MU synchrony varies considerably for different MU pairs in the same muscle (Bremner *et al.* 1991a; Nordstrom *et al.* 1992), and it is therefore necessary to sample from a number of MUs to obtain a reliable estimate. The latter condition is necessary because MU short-term synchrony is very weak, and trials of long duration are necessary to also improve reliability by increasing the number of counts in the cross-correlogram. These two conditions were satisfied in the present experiments, along with the use of a synchronization index (CIS) which is not influenced by MU firing frequency, unlike other indices used in previous studies (see Nordstrom *et al.* 1992). However, due to the technical difficulties of accurately recording the discharge times of more than one MU, it is not always feasible to satisfy these criteria in many experimental situations.

One technique utilised to overcome these difficulties is the surface EMG method, which estimates MU synchronization from the unrectified and full-wave rectified surface EMG which has been averaged with respect to the discharge of a single MU (Milner-Brown *et al.* 1973a). The surface EMG method has the advantage in that only a few MUs from one muscle need to be recorded, as it estimates MU synchronization from the population of active MUs within the muscle. If the strength of MU synchrony of each reference MU to the MU population is consistent, then the surface EMG method would give a reasonable estimate of global MU synchronization with as few as one reference MU, provided that the method is a valid one. However, the surface EMG method is a less direct estimate of MU synchrony than cross-correlation of MU discharge times. The limitations of this method are shared with all estimates involving the use of the surface EMG signal, in that the contribution of single MUs to the surface EMG are not equal (depending on location, size, number and orientation of muscle fibres), and variations in the contribution of single MUs to the surface EMG with time that are not necessarily related to a change in MU synchronization.

Using the surface EMG method, the present study has compared the estimate of MU synchronization from this technique to the more direct (but technically more difficult) cross-correlation procedure in the FDI muscle of 16 individuals. No significant relationship was

found between the synchronization index CIS and the surface EMG synchronization ratio (Fig. 5.5), indicating that the estimates of the strength of MU synchronization using the two methods are not equivalent. Given that cross-correlation of MUs is considered a reliable estimate of MU synchronization under optimal conditions (see above), this finding suggests two possibilities: 1) the surface EMG and cross-correlation methods are measuring different aspects of MU synchronization; and/or 2) the surface EMG method is subject to technical limitations rendering it an inaccurate estimate of MU synchronization within a muscle.

5.4.4.1 The surface EMG and cross-correlation methods: are they measuring the same phenomenon?

One explanation for differences in the estimate of MU synchronization between the surface EMG and cross-correlation techniques is that the two methods could be measuring different aspects of MU synchronization. MU cross-correlation measures the strength of synchronization between pairs of concurrently active MUs, whereas the surface EMG method measures synchronization between a reference MU and all other active MUs within the muscle, providing a more global estimate of MU synchronization. If the surface EMG method is technically sound, then it is possible to account for differences between the two estimates of MU synchrony based on these methodological differences. For example, there could be weak synchronization between individual MU pairs, but wide ranging across the motoneuron pool, giving a large surface EMG synchronization ratio. Alternatively, there could be strong synchronization between a MU pair, but each individual MU of the pair could have consistent differences in MU synchrony with all other MUs in the muscle, i.e. similar to that observed in Fig. 5.2. It would be feasible to assess this possibility by examining the strength of MU synchronization using the surface EMG method in each MU of a cross-correlated pair (e.g. MU A X MU B) and compare this with the *mean* strength of MU synchronization of these two MUs when cross-correlated with other MUs in the muscle (e.g. MU A X MU C, MU A X MU D; MU B X MU E, MU B X MU F). If MU A has a low surface EMG synchronization ratio, and MU B has a high surface EMG synchronization ratio, then the mean strength of MU synchronization from cross-correlation when

considering other active MUs should be low for MU A (i.e. weak synchronization for MU A X MU C and MU A X MU D) and high for MU B (i.e. strong synchronization for MU B X MU E and MU B X MU F) provided that the surface EMG method is valid. Examination of twenty cross-correlated MU pairs which exhibited such a phenomenon in the present study (i.e. had widely divergent surface EMG synchronization ratios [mean difference of 0.74; range, 0.26 to 1.6], and were cross-correlated with at least two other MUs [mean of 4 cross-correlograms per MU; range 2 to 8]), revealed a difference in the mean cross-correlated strength of MU synchronization between MU pairs of -0.028 extra discharges s^{-1} (range -0.4 to 0.3 s^{-1}). This was calculated by subtracting the mean strength of MU synchronization (measured from cross-correlation with other active MUs) of the MU with the smallest surface EMG synchronization ratio from the mean strength of MU synchronization (measured from cross-correlation with other active MUs) of the MU with the largest surface EMG synchronization ratio of the pair. The negative difference in the mean synchronization index CIS between MUs of each pair indicates that the MU with the larger surface EMG synchronization ratio of the pair usually did not exhibit the greatest synchronization index CIS when it was averaged with other MUs in the muscle. Using linear regression analysis on the same data, there was no significant relationship between the difference in the surface EMG synchronization ratio (the MU with the smallest surface EMG synchronization ratio was always subtracted from the MU with the largest) and the corresponding difference in the mean synchronization index CIS in the twenty MU pairs ($r^2 = 0.13$, $P > 0.05$). From a limited number of MUs, these results suggest that the surface EMG synchronization ratio between MU pairs is not simply related to the extent of MU synchrony revealed by cross-correlation of MU discharge. However, the surface EMG method estimates MU synchronization from one reference MU to all other active MUs in the muscle. As only a small number of cross-correlograms are usually available for one particular MU under experimental conditions, it is possible that the limited number of MUs which were recorded were not representative of the entire active MU population which are reflected in the estimate of MU synchronization using the surface EMG method. Given that the MU recordings in the present study were all made under low force conditions (all MU recruitment thresholds <

4 N) which limits the number of active MUs in the FDI, it suggests that this possibility is unlikely.

5.4.4.2 Evidence for technical limitations to the surface EMG method

A major limitation of the surface EMG method is that, on theoretical grounds (Milner-Brown *et al.* 1973a), slightly positive synchronization ratios would be expected under asynchronous conditions. This is due to the partial summation of the rectified waveform and the background EMG activity, and is commonly known as the artifact associated with signal rectification. This limitation was recognised originally by Milner-Brown *et al.* (1973a) who used a theoretical approach to calculate the contribution of the rectification artifact which accounted for changes in the signal-to-noise ratio. When subtracting the contribution of the rectification artifact from the synchronization ratio, the surface EMG technique has been shown to provide a sensitive measure of the level of MU synchronization within a population of neurons (Roscoe *et al.* 1985). However, due to the extra data processing required to calculate the rectification artifact, Milner-Brown *et al.* (1975) chose to simplify the method by assuming that the rectification artifact was fixed, and was independent of the signal-to-noise ratio. Despite this obvious limitation, an increase in MU synchronization with strength-training observed by Milner-Brown *et al.* (1975) using the method has been widely accepted in the literature.

Using results based on the computer simulation of 100 MUs discharging asynchronously, Yue *et al.* (1995) reported that the rectification artifact contributed from 0 to 15% of the synchronous activity, and varied non-linearly with the signal-to-noise ratio. From these experiments, two recommendations were made by these authors when using the simplified surface EMG method. The first recommendation was that the surface EMG technique only be used when the rectification artifact was negligible, which occurred when the peak rectified EMG signal was more than three times as large as the background EMG level. In the present study, only 12 of 189 MUs (range 1-6 reference MUs per muscle) in 6 muscles satisfied this rather stringent criterion. Using these MUs, there was also no significant relationship between the mean surface EMG ratio and the synchronization index CIS between muscles (r^2

= 0.35, $P > 0.05$). When the rectified EMG peak was more than twice as large as the background EMG level, still only 43 MUs (range 1-12 MUs per muscle) in 18 muscles were included, and this also failed to reveal a significant correlation with the mean synchronization index CIS values in those muscles ($r^2 = 0.02$). The low number of MUs satisfying these conditions suggests that they are difficult to achieve in an experimental situation in FDI. The second recommendation for using the simplified surface EMG method was that surface EMGs should be obtained during similar contraction levels (Yue *et al.* 1995). Most of the forces in the present study were between 1-5% MVC, with no contraction over 12% MVC. The small force differences observed in most of the contractions in the present study would produce a negligible difference in the rectification artifact between contractions (see Yue *et al.* 1995). Therefore, when the conditions for using the simplified surface EMG method were optimised, there was still no relationship between the two measures of MU synchrony, suggesting that the surface EMG method is not a useful index of MU synchronization. It is possible that these limitations can be minimised (see Yue *et al.* 1995), but these conditions are difficult to achieve in an experimental situation.

Theoretically, one of the main potential advantages of the surface EMG method is that less MUs need to be recorded in a single experiment, as it represents a more global estimate of MU synchrony in the muscle than the cross-correlation of MU pairs. One observation in the present study supports the contention that the surface EMG method does not give a reliable estimate of overall synchrony if only one or a few MUs are used as a reference, even though it is the population of MUs which contribute to the surface EMG averages. In Fig. 5.2, surface EMG synchronization ratios are provided for two MUs in the same muscle, during the same contraction. Although cross-correlation of both MUs resulted in quite high MU synchronization (Fig 5.2A), very different surface EMG estimates of MU synchrony were obtained when each MU was used as a separate reference. The strength of MU synchronization using the surface EMG method was more than 3 times greater in Fig. 5.2C compared to Fig. 5.2B. Apart from methodological considerations (see above), technical problems (such as the size of the surface EMG representation of the MU, i.e. signal-to-noise ratio), are likely to be responsible for this effect. For example, the area due to synchronous

firing of other MUs (black area Fig. 5.2B,C) is similar in both reference MUs. However, the surface EMG representation of the reference MU in Fig. 5.2B is much greater than the MU in Fig. 5.2C, producing widely divergent surface EMG synchronization values. Therefore, as previously shown by Yue *et al.* (1995), the estimate of MU synchronization from the surface EMG is highly dependent on the signal-to-noise ratio.

5.4.2 MU synchronization in trained individuals

It has previously been demonstrated using the simplified surface EMG method that MU synchronization is two to three times stronger in weightlifters compared to untrained subjects (Milner-Brown *et al.* 1975). Using the same method, this association between strength-training and MU synchronization was not observed in the present study (Fig. 5.3A). MU synchronization was greater in strength-trained subjects, but only when using the cross-correlation technique, and only compared to skill-trained subjects who exhibited the lowest MU synchronization (Fig. 5.3B). In the present study, there was no difference in MU synchronization between strength-trained and untrained subjects using both surface EMG and cross-correlation methods (cf. Chapter 4). MU synchronization was still higher in strength-trained compared to untrained subjects, but the removal of MUs which could not be matched with an appropriate surface EMG signal weakened the difference (Fig. 5.3B), as the comparison was not sufficient to reach statistical significance (Scheffe's F-test, $P = 0.07$). Nevertheless, similar findings have been established for the cross-correlation procedure when all MU pairs were considered (Chapter 4) suggesting that the MUs used in the present study are representative of the total sample.

Two possibilities exist to explain why the two- to three-fold difference in the surface EMG synchronization ratio between weightlifters and control subjects (Milner-Brown *et al.* 1975) was not detected in the present study. Firstly, differences in the surface EMG synchronization ratio between trained groups may simply be due to differences in the mean levels of muscle activation, which would result in different numbers of active MUs in the muscle (Yue *et al.* 1995). The mean contraction levels were similar between all groups in the present study (0.04 N difference between groups) and there were no significant differences

in the surface EMG ratio between groups. The mean contraction levels for weightlifters and control subjects in the Milner-Brown *et al.* (1975) study were not reported. Secondly, the level of strength-training of the weightlifters may have differed between the two studies. The strength-trained individuals used in the present study participated in strength-training activities on average 8 hrs/week for four years (range; 4-14 hrs/week, 2-6 yrs). It is possible that the weightlifters used in the Milner-Brown *et al.* (1975) study were more extensively trained, and the extra training could be responsible for the greater MU synchronization in these individuals. However, the MUs used to calculate the surface EMG synchronization ratio in the present study showed greater synchronization with cross-correlation and not with the surface EMG method, suggesting that this possibility is unlikely.

5.4.3 The width of the central synchronous peak

Using both surface EMG and cross-correlation analysis, the duration of synchrony was narrower in skill-trained subjects (Fig. 5.6). In the cross-correlogram, a narrow central synchronous peak is believed to arise from common-stem pre-synaptic inputs that increase the probability of simultaneous discharge in the target neurons sharing these inputs (Kirkwood & Sears, 1982; Datta & Stephens, 1990). If the common input arises from a group of neurons which are themselves synchronized, this would broaden the peak in the cross-correlogram over a much wider time period (Kirkwood *et al.* 1982). However, a relationship between the width of the peak and the type of common input has only been established from the cross-correlogram, and it is unknown whether the width of the surface EMG peak is a reflection of the level of common input along the corticospinal pathway. Both measures of MU synchrony revealed narrower peaks in skill-trained subjects, and it is tempting to suggest that they are measuring the same physiological phenomenon. However, no relationship existed between the peak width measured from the rectified surface EMG and the cross-correlogram for estimates of synchrony in single muscles (Fig. 5.6). Irrespective of this, similar peak width durations were detected using both methods, which adds to the speculation that they are both reflecting MU short-term synchrony. As expected, the peaks were generally broader using the surface EMG method, because the surface EMG

contribution of MUs is broader than those of single MU action potentials. Broad duration synchronous peaks (> 40 ms) found in Parkinson's disease patients also appear to be of similar duration using the surface EMG (Milner-Brown *et al.* 1975) and cross-correlation procedures (Dengler *et al.* 1986; Baker *et al.* 1992).

In summary, there is a poor correlation between global estimates of MU synchronization in a muscle using MU cross-correlation and surface EMG methods. Cross-correlation of MU discharge times is a more direct, and therefore more reliable measure of MU synchronization, provided that sufficient MU pairs are included in the analysis. In contrast, evidence has accumulated (Yue *et al.* 1995; present study) that the estimation of MU synchronization from the surface EMG is subject to significant technical problems. These methodological problems are recognised, but are difficult to avoid under experimental conditions, suggesting that the surface EMG method is of limited usefulness as an indicator of overall MU synchronization in a muscle. The present study, and that of Yue *et al.* (1995), cast some doubt on the use of the surface EMG method for quantitative measurement of MU synchrony. For this reason, the relationship between strength-training and increased MU synchrony reported by Milner-Brown *et al.* (1975) is open to question. Like Milner-Brown *et al.* (1975) I found a tendency for higher MU synchrony in strength-trained subjects (Chapter 4). However, this was true for the MU cross-correlation data, but not with the surface EMG method.

CHAPTER 6

HEMISPHERIC DIFFERENCES IN MOTOR CORTEX EXCITABILITY DURING SIMPLE INDEX FINGER ABDUCTION

6.1 Introduction

Transcranial stimulation of the motor cortex using TMS or TES stimulators are powerful techniques for assessing the integrity and operation of the fast corticospinal pathway in humans (Rothwell *et al.* 1991). Several previous studies in man have reported that hand preference is associated with asymmetries in the ability to activate corticospinal neurons controlling small hand muscles with TMS under resting conditions. The hemisphere controlling the dominant hand was found to have a larger cortical representation for the target muscle (Wassermann *et al.* 1992) and a lower threshold for a MEP in passive muscle (Macdonell *et al.* 1991; Triggs *et al.* 1994). In these three studies, TMS was used to examine the excitability of the corticospinal pathway while the muscles were relaxed. The differences between sides revealed with TMS in the passive state reflect the "capacity" of the corticospinal system to activate corticospinal neurons controlling the hand muscles of each side. These factors includes differences in number, efficacy or activity of excitatory and inhibitory inputs to corticospinal neurons that are activated by TMS, different effectiveness of corticospinal inputs on the motoneuron pools, or even differences in the resting excitability of segmental interneurons and motoneurons. While these findings are of interest, it is of greater functional importance to establish the relative contribution of the corticospinal neurons in the two hemispheres during the voluntary activation of their target muscles. The pattern or extent of corticospinal neuron activity while the hand is being used might reasonably be related to differences in fine motor skill in preferred and non-preferred

hands.

In the present study I have used TMS and TES to assess hemispheric differences in excitability of corticospinal neurons during active voluntary contraction of the FDI muscle in dominant and non-dominant hands of RH subjects. This was accomplished by between-hand comparisons of the extent of facilitation of the MEP produced by TMS and TES delivered at passive threshold strength as index finger abduction was performed at various target forces. When a muscle is activated in a voluntary contraction the MEP following TMS and TES increases in size, due to increased excitability of corticospinal and alpha motoneurons (Hess *et al.* 1987; Maertens de Noordhout *et al.* 1992; Ugawa *et al.* 1995) related to their voluntary activation in the task. As TES is believed to activate corticospinal neurons directly, and TMS activates the corticospinal pathway trans-synaptically (reviewed in Rothwell *et al.* 1991), the responses to TMS should include a greater component due to increased excitability of corticospinal neurons as the muscle is activated voluntarily. If there are hemispheric differences in the activity of corticospinal neurons during task performance depending on which hand is used, I would expect to see an asymmetric pattern of contraction-induced facilitation of the MEP in FDI of the two hands with TMS, but not TES.

This investigation was prompted by the earlier observation that when FDI muscle is activated during index finger abduction, MU short-term synchronization in FDI is significantly lower in the dominant hand of RH subjects than in the non-dominant hand, and in both hands of LH subjects (Chapter 2). Several lines of evidence implicate corticospinal neurons in the generation of MU short-term synchronization in man (Farmer *et al.* 1990; Datta *et al.* 1991; Farmer *et al.* 1993b). One possible explanation for the earlier finding of reduced MU synchronization in the dominant hand of right-handers is that the corticospinal neurons were less active during the task when it was performed with the dominant hand. The present experiments using TMS and TES were designed as a more direct test of this hypothesis.

6.2 Methods

TMS was used to study MEPs produced in right and left FDI in 8 healthy subjects (7 males) ranging in age from 20 to 38 years. In five of these subjects, experiments were repeated using TES. MU synchronization data from the dominant and non-dominant hand in four of these subjects were obtained in Chapter 2. Experiments were performed with the subjects' informed consent and with the approval of the Ethics Committee for Human Experimentation at the University of Adelaide. The hand used for writing was designated the dominant hand, and in each subject this was the right hand. The degree of laterality was assessed by questionnaire using the Edinburgh Handedness Inventory (Appendix A). A LQ was calculated on the basis of answers to the questionnaire, with a value of 1 indicating strong right-handedness, a value of -1 indicating strong left-handedness, and a value of 0 indicating no consistent hand dominance. All 8 subjects were right-hand dominant with a mean LQ of 0.87 (range 0.5 - 1.0).

6.2.1 Experimental apparatus

Subjects were seated in a dental chair with a head rest and neck support which restricted head movement (Plate 6.1). The right or left arm and hand was secured in a manipulandum, the details of which has been described previously (Chapter 2). The distal interphalangeal joint of the index finger was aligned with a load cell which measured the force of abduction. The index finger abduction force signal (bandwidth 0 - 5 kHz) was recorded on FM tape (Vetter model 400D, 22 kHz/ch). The surface EMG of the left and right FDI was recorded with bipolar Ag-AgCl electrodes placed 2 - 3 cm apart, with the active electrode placed at the motor point and the inactive electrode placed on the metacarpophalangeal joint. Surface EMG signals were amplified (200 - 1000X), filtered (5 Hz - 1 kHz), digitised online on a personal computer (2 kHz sampling rate) and recorded on tape. The maximal M-wave of each FDI was established through supramaximal electrical stimulation of the ulnar nerve with bipolar Ag-AgCl electrodes placed 3 - 4 cm apart running longitudinally along the distal and medial aspect of the forearm. Electrical M-wave stimuli were applied at the wrist with a Digitimer D180 electrical stimulator. The maximum output of the stimulator was 750 V, and

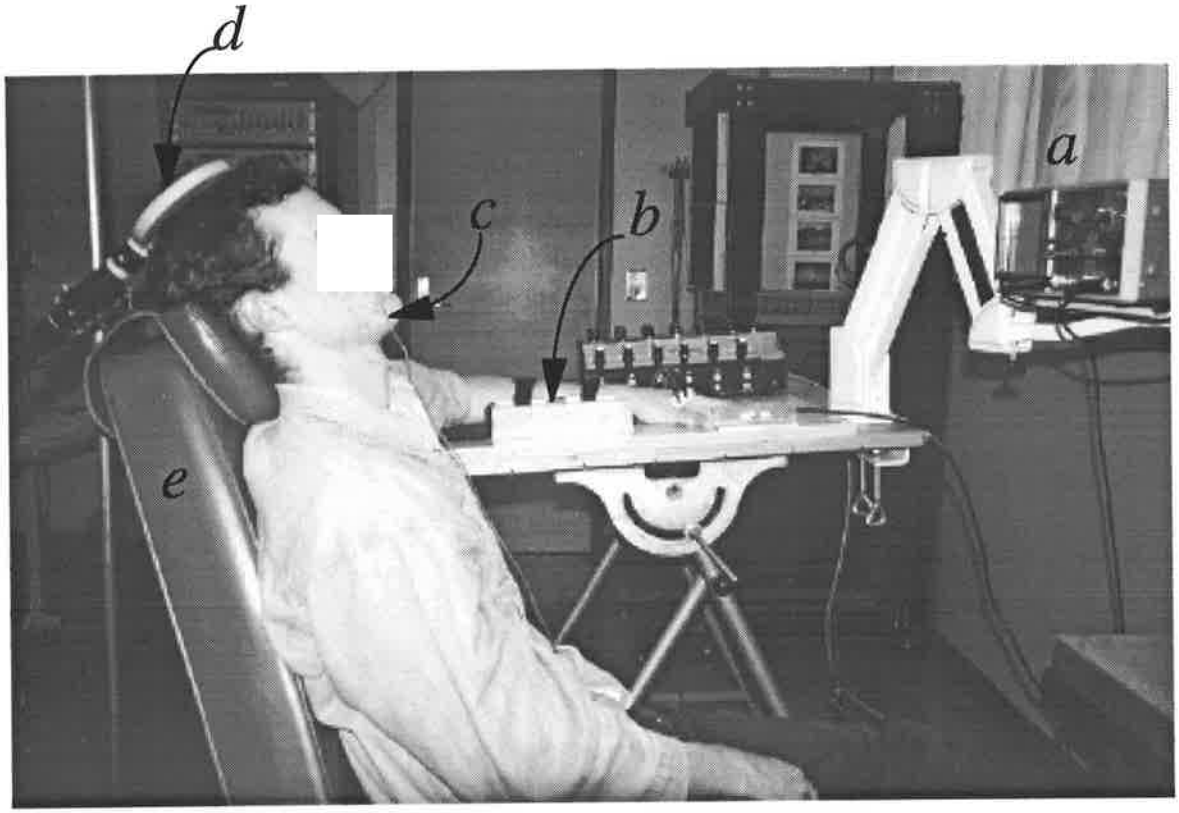

Plate 6.1. A subject seated with their left arm secured in the manipulandum during transcranial magnetic stimulation.

Subjects were seated in a dental chair with a head rest and neck support which minimised head movement. The subjects' hand and arm were secured in the manipulandum, and they were shown the output of the load cell on an oscilloscope screen which was positioned in front of them at eye-level. Surface electromyogram electrodes were attached to the skin overlying the first dorsal interosseous muscle and an earth electrode was attached to the lip of the subject. Transcranial magnetic stimulation was applied through a 90 mm circular coil centred at the vertex of the scalp and held tangential to the skull in an antero-posterior orientation (handle posterior). The position of the coil was constantly monitored with respect to the marks placed on the scalp to ensure that there was no change in the site of stimulation.

The labelled components are: ***a***; visual display,
b; manipulandum,
c; 'lip clip' ground electrode,
d; circular magnetic stimulating coil,
e; dental chair.

the stimulus intensity was expressed on a linear scale as a percentage of the maximum output.

6.2.2 *Protocol 1: Contraction induced facilitation of MEPs with TMS*

Responses to TMS were recorded in left and right FDI muscles of all eight subjects in the same experimental session. The hand to be tested first in a session was chosen at random. The hand was secured in the manipulandum and the subject was provided with visual feedback of the index finger abduction force on an oscilloscope screen. The subject was asked to perform maximal index finger abduction, with care taken to minimise contribution from other muscles. The largest of three attempts was taken as MVC for index finger abduction. The maximal M-wave was then obtained in relaxed FDI by supramaximal electrical stimulation of the ulnar nerve (average of responses to five stimuli at < 0.5 Hz, pulse duration 100 μs). Supramaximal ulnar nerve stimulation was elicited in all subjects at 16 - 30% (120 - 225 V) maximum stimulator output.

TMS was applied with a Magstim 200 magnetic stimulator through a 90 mm circular coil (20/trial, < 0.2 Hz) centred at the vertex of the scalp (see Plate 6.1). The magnetic stimulus produces a magnetic field at the centre of the coil in the order of 2 Tesla (Hess *et al.* 1987). The magnetic field generated by the coil passes unattenuated through structures such as the scalp and the skull, and induces a current in the brain which reaches a peak at 200 μs. The induced current flows in the brain in a direction opposite to that in the coil and in a plane parallel to that of the coil. The optimal direction of current flow in the coil was dependent on the hemisphere to be activated. An anti-clockwise current in the coil (viewed from above) was used to activate the right side muscles (left motor cortex) and a clockwise current in the coil was used to activate the left side muscles (right motor cortex). Intensities were expressed as a percentage of the maximum output of the stimulator. The coil was initially placed at the vertex and the optimal scalp position for TMS was determined by moving the coil from this position and observing the site at which the largest MEP was produced in relaxed FDI using weak suprathreshold TMS. The optimal scalp position was marked and the stimulating coil was fixed at this location on the scalp using a clamp and external support.

The threshold stimulus strength for a MEP in relaxed FDI was then determined using 2% increments of stimulator output. Passive threshold was defined as the lowest intensity of TMS for which 3 out of 5 stimuli evoked a MEP of amplitude greater than 50 μV in resting FDI, which is a similar definition to that used by previous investigators (Datta *et al.* 1989; Mazzocchio *et al.* 1994; Triggs *et al.* 1994; Schieppati *et al.* 1996). TMS at passive threshold strength (20/trial, < 0.2 Hz) were then applied with the FDI at rest and while the subject performed isometric index finger abduction at various static target forces (0.5 N, 1.0 N, 2.0 N, 3.5 N, 5.0 N), as well as 25% and 50% of the subject's MVC for index finger abduction. Subjects were instructed to match the target force as closely as possible using visual feedback. The order of contractions was randomised for force levels of 0.5 N to 5 N. To minimise the effects of fatigue, the contraction levels of 25 and 50% MVC were performed last and with an intermittent 50% duty cycle of activation. During these trials, the subject was given audio cues which indicated when to contract and relax the FDI muscle. TMS was given 2-s into the 3-s contraction, with a 3-s rest between contractions. Once the averaged MEPs had been obtained for the series of target forces with one hand, the stimulating coil was reversed to change the direction of current flow, and the protocol was repeated for the opposite hand. The head and coil position was constantly monitored throughout the experiment by one investigator, and care was taken to ensure that the coil position did not stray from the optimal scalp location for trials at the different target forces.

6.2.3 Protocol 2: Contraction induced facilitation of MEPs with TES

Five of these eight subjects (mean LQ = 0.83, range 0.5 - 1) were tested in a second session on a separate day using TES and a similar protocol as in the experiments using TMS. Responses to TES were obtained in both hands in the same experimental session. TES was applied with a Digitimer D180 electrical stimulator. Stimuli were delivered via two 9-mm diameter surface electroencephalographic (EEG) electrodes filled with conducting gel and fixed on the scalp with collodion at the vertex (cathode) and approximately 7 cm laterally (anode). A anode was fixed to the scalp on either side of the vertex, with the active anode dependent on which hemisphere was to be stimulated. Optimal positions for the anode were

established in preliminary trials in each subject using a hand-held stimulator consisting of two saline-soaked pads.

Passive threshold intensity for TES was established in resting FDI in all but one subject using the criteria previously described. In the subject in whom MEPs could not be elicited in resting FDI using TES, the threshold stimulus strength for a MEP at the 0.5 N contraction level was used instead for all TES trials at various contraction levels. Stimulus intensities for TES ranged from 25 - 95% of the maximum stimulator output of 750V. Subjects contracted the FDI at the same force levels used for the TMS trials while TES (10/trial, < 0.5 Hz, 50 - 100 μs pulse duration) were applied to the contralateral hemisphere. The final procedure for each hand was supramaximal stimulation of the ulnar nerve to obtain a maximal M-wave in FDI (average of 5 trials). The anode was then changed to the opposite hemisphere and the target contraction levels were repeated for the other hand while TES was applied.

6.2.4 Data Analysis

Averaged MEPs were obtained from FDI following TMS (n=20) and TES (n=10) at each target contraction level and also in resting muscle. The MEP areas were measured from the digitised records and normalised as a percentage of the area of the maximal FDI M-wave in that hand.

Data are presented as mean ± S.D., unless otherwise stated. Paired t-tests were used for comparisons between dominant and non-dominant hands for threshold stimulation intensity and normalised MEP area in the resting condition. An ANOVA was employed for comparisons between stimulation type (TMS, TES), hand dominance (dominant, non-dominant) and contraction level (0.5 N to 50% MVC). For all statistical comparisons, significance was reported for $P < 0.05$.

6.3 Results

Mean MVC for index finger abduction was 38.4 ± 8.5 N using the non-dominant hand and

39.6 ± 12.9 N using the dominant hand in the eight subjects. These values were not significantly different (paired t-test, $P > 0.05$). Mean maximal M-wave areas were not significantly different between non-dominant (37.7 ± 23.1 mV.ms) and dominant (42.7 ± 16.6 mV.ms) hands in the thirteen experimental sessions (paired t-test, $P > 0.05$; $n = 13$).

Threshold strength for a MEP in resting FDI using TMS ranged from 34 - 58% of maximum stimulator output in the eight subjects. Mean passive threshold strength using TMS was 43 ± 8% for FDI in the non-dominant hand and 41 ± 3% in the dominant hand, a non-significant difference (paired t-test, $P > 0.05$, $n = 8$). There were no significant differences between hands in the size of normalised MEPs evoked in resting FDI by TMS at passive threshold strength (non-dominant *vs.* dominant; 1.0 ± 1.2% of maximal M-wave area *vs.* 0.6 ± 0.7%; paired t-test, $P > 0.05$) or passive threshold TES (non-dominant *vs.* dominant; 0.6 ± 0.2% of maximal M-wave area *vs.* 0.8 ± 0.4%; paired t-test, $P > 0.05$, $n = 4$).

The mean latency of the MEP using passive threshold TMS was 23.4 ± 1.4 ms ($n = 16$) with the FDI relaxed and 21.9 ± 1.8 ms ($n = 112$) in active muscle. There was no difference in MEP latency for relaxed (22.0 ± 1.6 ms, $n = 8$) and active (21.9 ± 1.2 ms, $n = 56$) muscles using TES. There were no significant differences in MEP latencies between hands with either stimulation technique in either passive or active muscle (paired t-tests, $P > 0.05$).

Averaged MEP responses in FDI of both hands following passive threshold TMS and TES under passive and active conditions are shown for one subject in Fig. 6.1. With both TMS (Fig. 6.1A) and TES (Fig. 6.1B), MEP size increased with increasing muscle activation. This was a universal finding in all subjects. In this subject, the normalised MEPs with TMS were consistently larger in the non-dominant hand at each active contraction level (Fig. 6.1A), ranging from 15 times higher than the dominant hand in the weakest contraction (0.5 N) (normalised MEP area 17.8% *vs.* 1.2%) to 1.5 times higher (70.8% *vs.* 53.1%) in the strongest (50% MVC). There was no consistent difference in MEP area between hands in active FDI using TES in this subject (Fig. 6.1B) or any of the other four

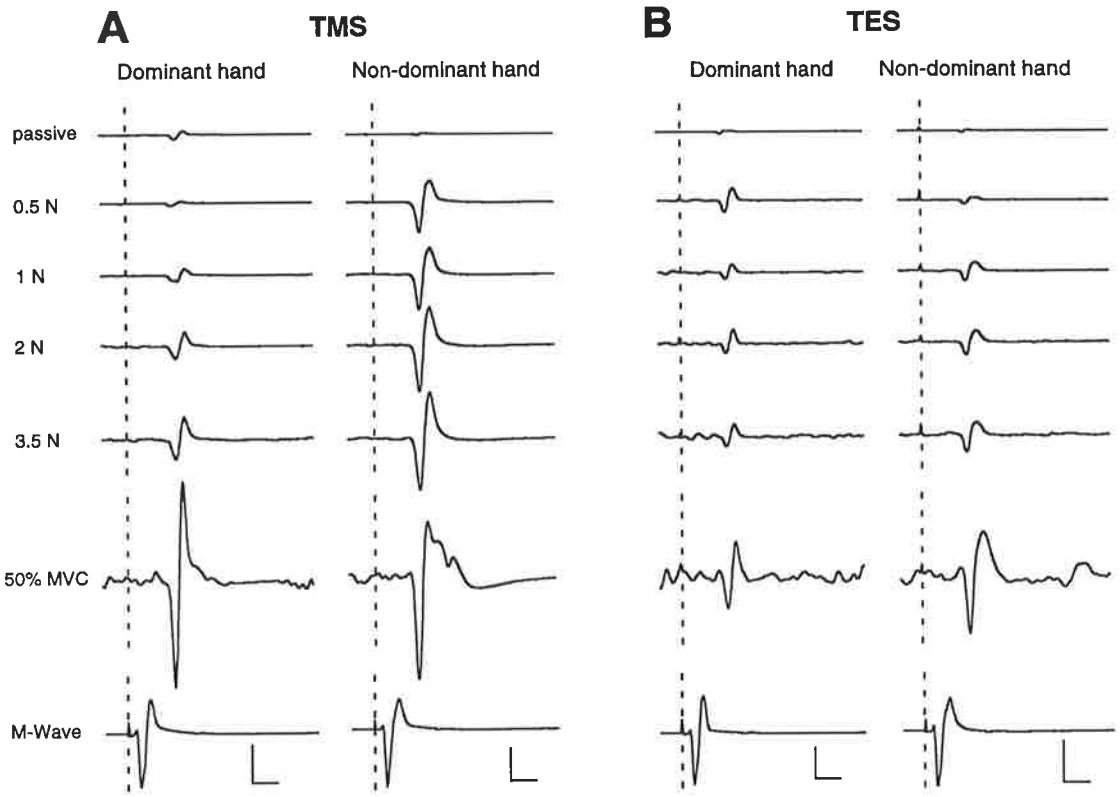

Figure 6.1 Contraction-induced facilitation of muscle evoked potentials from first dorsal interosseous in dominant and non-dominant hands of one subject following transcranial magnetic and electrical stimulation.

A, TMS at passive threshold strength. Averaged MEPs (n = 20) for the dominant (left panel) and non-dominant (right panel) hand are shown for the passive condition (top) and five different levels of voluntary isometric index finger abduction (below), ranging from 0.5 N to 50% MVC. The lowermost trace is the maximal M-wave in FDI for that hand. TMS strength was 36% of maximum stimulator output for both hemispheres. The dashed vertical lines represent the stimulus onset. ***B***, TES at passive threshold strength. Averaged MEPs (n = 10) for the dominant (left panel) and non-dominant (right panel) hand are shown for the corresponding trials in the same subject using TES. Data arranged as in A. Horizontal calibration bars = 10 ms. Traces in each column have been scaled so that the maximal M-waves are the same size. Vertical calibration bars = 1.25 mV for traces passive to 50% MVC, and 5 mV for maximal M-wave. With TMS, the MEP was consistently larger in the non-dominant hand compared to the dominant hand, particularly at low force levels. No consistent difference between hands was observed with TES.

subjects in whom TES was used.

During index finger abduction, a three-way ANOVA (stimulation type, hand dominance, contraction level) revealed significant effects for stimulation type ($F[1, 154]=13.9$, $P < 0.001$), contraction level ($F[6, 154]=27.4$, $P < 0.0001$), and the stimulation type-hand dominance interaction ($F[1, 154]=4.9$, $P < 0.05$). Hand dominance as a dependent variable by itself just failed to comply with the designated statistical significance level in the three-way ANOVA ($F[1, 154]=3.9$, $P=0.05$). These results enabled separate two-way ANOVA comparisons for stimulation type and hand dominance (each with contraction level) to be performed. These have been considered separately below.

The pooled data from the eight subjects obtained using TMS are summarised in Fig. 6.2. The mean normalised MEP area increased monotonically with muscle activation level in each hand. Contraction level had a significant effect on normalised MEP area in the two-way ANOVA ($F[6,98] = 17.3$, $P < 0.001$). At each level of active contraction the mean normalised MEP was larger in the non-dominant hand. Two-way ANOVA (dominance, contraction level) revealed that the extent of facilitation of the MEP using TMS in active muscle was significantly different in dominant and non-dominant hands ($F[1,98] = 10.0$, $P < 0.005$). The relative differences were larger at low target forces, with the ratio of normalised MEP areas (non-dominant/dominant) ranging from 2.1 ($13.2 \pm 3.5\%$ *vs.* $6.4 \pm 2.1\%$) in the weakest contraction (0.5 N) to 1.2 ($60.7 \pm 7.3\%$ *vs.* $50.8 \pm 6.9\%$) in the strongest (50% MVC). The effect of hand dominance on the extent of MEP facilitation was consistent across all activation levels with TMS (the interaction of dominance and contraction level was not significant in the two-way ANOVA; $F[6,98] = 0.3$, $P > 0.05$).

With TES, the pooled data from the five subjects tested revealed no significant difference in the extent of MEP facilitation with muscle activation in the two hands (two-way ANOVA; $F[1,56] = 0.03$, $P > 0.05$). As with TMS, there was a significant effect of contraction level on the extent of MEP facilitation ($F[6,56] = 14.0$, $P < 0.001$). The interaction (dominance x contraction level) was not significant in the ANOVA ($F[6,56] = 0.8$, $P > 0.05$). These results using TES, which predominantly excites corticospinal axons directly, provides

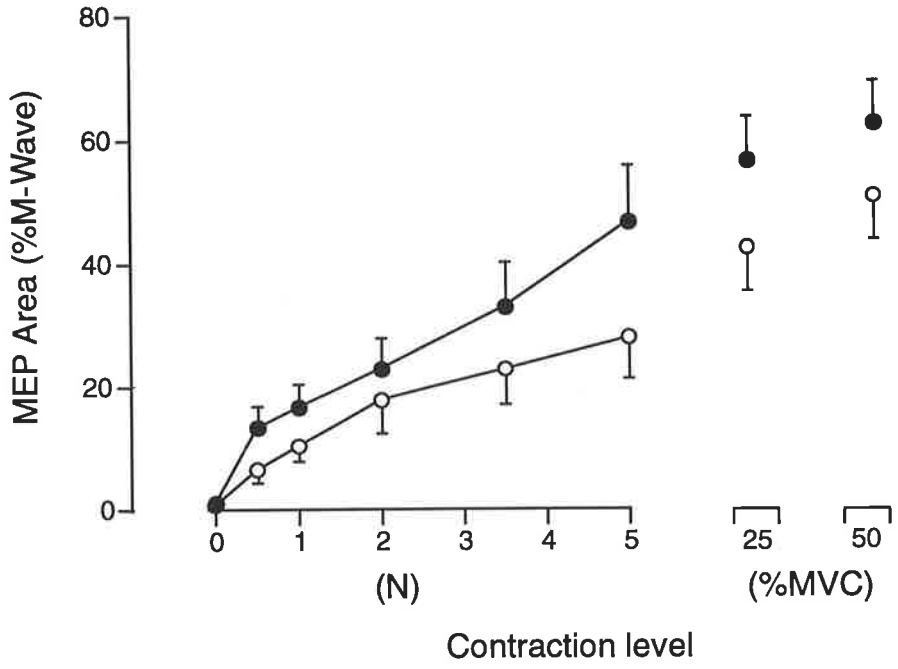

Figure 6.2. Contraction-induced facilitation of muscle evoked potentials following transcranial magnetic stimulation was larger in the non-dominant hand at each active force level in pooled data.

Mean (± S.E.) normalised MEP areas from dominant (open circles) and non-dominant (filled circles) hands of 8 right-handed subjects following passive threshold TMS at various levels of voluntary contraction. The horizontal axis shows the force of index finger abduction. Mean normalised MEP area increased monotonically with increasing contraction force, and at each force level the mean normalised MEP was larger in the non-dominant hand. The extent of contraction-induced facilitation of the MEP using TMS was significantly different in dominant and non-dominant hands (two-way ANOVA, $P < 0.005$).

evidence that the difference in MEP facilitation between hands with muscle activation revealed using TMS are not due to differences in spinal alpha motoneuron excitability.

The effect of hand dominance on the extent of MEP facilitation was not consistent for all subjects, as the interaction (subject x hand dominance) was significant in the two-way ANOVA ($F[7,96] = 2.8$, $P < 0.01$). In four subjects, the amount of MEP facilitation using TMS was consistently larger for the non-dominant hand at the different levels of active contraction in FDI, and a paired t-test on data from each subject (pooled for all active contraction levels) revealed significant differences in normalised MEP between hands (all $P < 0.01$). In one subject, MEP facilitation was significantly larger for the dominant hand over all force levels (paired t-test; $P < 0.01$). For the remaining three subjects the extent of MEP facilitation using TMS was similar in the two hands at each force level.

Responses to TMS are influenced by the excitability of corticospinal neurons in motor cortex, in addition to spinal alpha motoneuron excitability. The present results suggest that the differences in MEP facilitation between hands using TMS are related to increased excitability of corticospinal neurons when the non-dominant hand is used for the task. Under the present experimental conditions of stimulation at passive threshold, therefore, I would expect the extent of MEP facilitation with TMS to be greater than with TES in each hand, reflecting the activation of a population of corticospinal neurons in the task and increased excitability of the active corticospinal neurons, a larger corticospinal volley evoked by TMS, and a larger MEP. The difference in the amount of facilitation of the MEP with TMS and TES in each hand when the muscle is activated is a measure of the increased size of the stimulus-evoked corticospinal volley due to involvement of corticospinal neurons in the task. This comparison is shown in Fig. 6.3. For the non-dominant hand (Fig. 6.3A), the normalised MEP area obtained using TMS was consistently larger than that obtained using TES at each contraction level, and the differences between the two stimulation techniques were significant (two-way ANOVA; $F[1, 77] = 15.9$, $P < 0.001$). The largest relative difference was seen with the 2 N contraction, for which the ratio of normalised MEP areas with the two stimulation techniques (TMS/TES) was 2.85. The

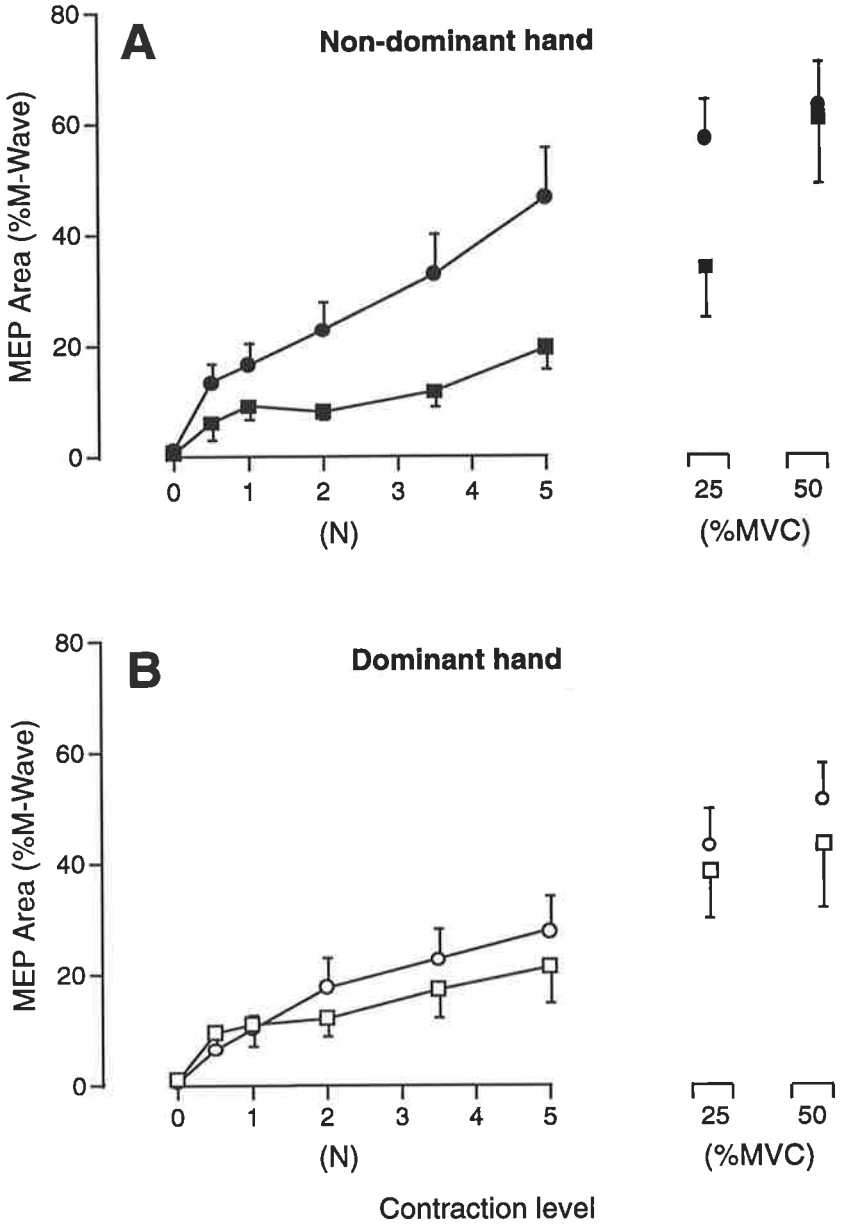

Figure 6.3 Comparison of contraction-induced facilitation of muscle evoked potentials in each hand with transcranial magnetic and electrical stimulation.

A, Mean (± S.E.) normalised MEP areas in FDI of the non-dominant hand in 8 right-handed subjects following TMS (filled circles) and 5 subjects following TES (filled squares) at various levels of voluntary contraction. ***B***, Data from the dominant hand in these subjects using TMS (open circles) and TES (open squares). In the non-dominant hand the normalised MEP was consistently larger following TMS than TES, and the differences between the two stimulation techniques were significant (two-way ANOVA, $P < 0.001$). In the dominant hand the differences between the two stimulation techniques were generally in the same direction but smaller, and were not statistically significant (two-way ANOVA, $P > 0.05$).

difference was smaller at the highest contraction levels. For the 25% MVC the ratio was 1.69, and it was 1.01 for the 50% MVC.

For the dominant hand (Fig. 6.3B), mean normalised MEP area was larger with TMS than TES for 5 of 7 active contraction levels, but the differences were less marked than in the non-dominant hand and were not significant overall (two-way ANOVA; $F[1, 77] = 1.3$, $P > 0.05$). The largest ratio of normalised MEP areas (TMS/TES) was 1.46 for the 2 N contraction, and the smallest was 0.70 at 0.5 N. As with the non-dominant hand, the differences between TMS and TES were smaller at the higher force levels (TMS/TES ratios 1.11 at 25% MVC and 1.18 at 50% MVC).

In a recent study of six RH subjects I found that the mean strength of MU synchronization in FDI was significantly weaker in the dominant hand (Chapter 2). A total of 199 MU pairs were used for this comparison. The mean (± S.E.) strength of FDI MU synchronization in the non-dominant hand was 0.39 ± 0.03 ($n = 111$) extra synchronous discharges s^{-1} and in the dominant hand it was 0.23 ± 0.03 s^{-1} ($n = 88$). In that study, isometric index finger abduction was used to activate FDI MUs, with most contractions in the range 0.5 N and 3.5 N, and none above 4 N. The difference in MU synchronization between hands may reflect differences in corticospinal neuron activity during the task, and this earlier finding prompted the present series of experiments using brain stimulation as a more direct test of this hypothesis. For comparison with the MU synchronization data, I have calculated the mean normalised MEP area obtained using TMS in each hand for the comparable range of forces used in the MU experiments, by pooling MEP data within the force range 0.5 - 3.5 N. Mean (± S.E.) normalised MEP area using TMS was $21.3 \pm 2.8\%$ ($n = 32$) in FDI of the non-dominant hand and $14.2 \pm 2.3\%$ ($n = 32$) in the dominant hand. The ratio of the mean strength of FDI MU synchronization in the non-dominant and dominant hands (1.7) is similar to the ratio of the normalised MEPs in FDI of these hands (1.5). Four subjects in the present study were part of the earlier MU study. Linear regression revealed a positive relationship between the non-dominant/dominant ratio of normalised MEP areas (pooled for the 0.5 - 3.5 N contractions) in each subject and the ratio of the strength of FDI MU

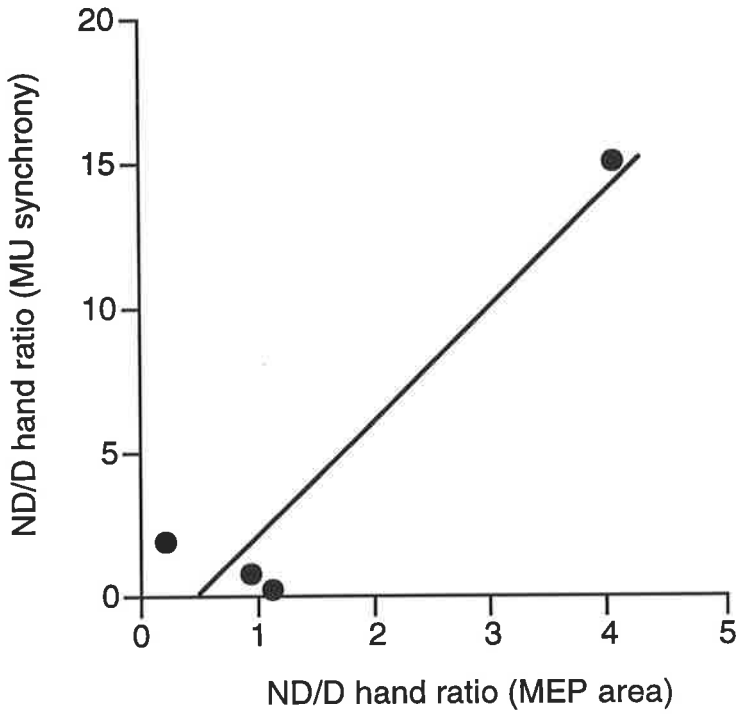

Figure 6.4 Comparison of the non-dominant/dominant hand ratio of normalised MEP areas and the ratio of the strength of FDI MU synchronization in the two hands for the same 4 subjects.

Non-dominant (ND)/dominant (D) hand ratio of the mean normalised MEP areas (pooled for the 0.5 N to 3.5 N contractions) *vs.* the ND/D ratio for the mean strength of MU synchronization (data from Chapter 2) in the same 4 subjects. Linear regression revealed a positive relationship ($r^2 = 0.9$, $P = 0.05$) between normalised MEP areas and MU synchrony for the ND/D hand ratio in these subjects.

synchronization in the two hands (Fig. 6.4, $r^2 = 0.9$, $n = 4$, $P = 0.05$). Taken together, these data suggest that a common physiological process contributes to the differences in MU synchronization and normalised MEP area in the FDI of each hand.

6.4 Discussion

The main finding in the present study was that the contraction-induced facilitation of the MEP in FDI was significantly larger in this group of right-handed subjects when the non-dominant hand was used for index finger abduction, but only with TMS and not TES. The similarity of the contraction-induced facilitation of the MEP in each hand using TES suggests that differences in spinal motoneuron excitability are not responsible for the differences seen using TMS. The differences between hands seen with TMS are likely to reflect greater corticospinal neuron activation during the task when it is performed with the non-dominant hand. While this was true for the group as a whole, one subject had larger MEP facilitation with TMS using the dominant hand. This suggests that hand preference is an important, but not exclusive, factor influencing the degree of corticospinal involvement in this task.

6.4.1 Contraction-induced facilitation of MEPs with TMS and TES.

TMS or TES of the motor cortex produces EMG responses in contralateral limb muscles which have a latency consistent with activation of a fast-conducting, monosynaptic corticospinal pathway (Rothwell *et al.* 1991). The CM projection is responsible for the earliest part of the MEP, but the later part of the MEP may be influenced by inputs from segmental interneurons activated by the corticospinal volley (Nielsen *et al.* 1993; Burke *et al.* 1994). TES predominantly activates corticospinal axons directly (Amassian *et al.* 1987), although recent evidence suggests that TES can also activate corticospinal neurons at the initial segment (Rothwell *et al.* 1994). The preferential activation of corticospinal axons with TES means that responses to TES are relatively insensitive to corticospinal neuron excitability. In contrast, responses to TMS are much more dependent on corticospinal neuron excitability, as the magnetic stimulus is believed to activate corticospinal neurons trans-synaptically (via cortico-cortical and/or thalamo-cortical fibre systems), or directly, at a

site near the soma (Rothwell *et al.* 1991). A number of studies have reported task-related differences in the size of MEPs produced by TMS (Datta *et al.* 1989; Flament *et al.* 1993; Schieppati *et al.* 1996), that exceed those seen with TES. The larger MEPs in different tasks are interpreted as evidence of task-related alteration in excitability of corticospinal neurons during performance of the task, due to increased corticospinal neuron discharge, and hence a larger corticospinal volley evoked by TMS. This interpretation has received recent support by direct recordings of corticospinal volleys from the medullary pyramid of a monkey performing a precision grip task (Baker *et al.* 1995). The corticospinal volley produced by TMS over the motor cortex was modified during the task, but that produced by electrical stimulation of the cerebral peduncles was not.

It is known that increasing levels of voluntary activation of a muscle results in a large, monotonic increase in size of the MEP produced by both TMS and TES (Hess *et al.* 1987; Maertens de Noordhout *et al.* 1992; Ugawa *et al.* 1995). In addition, the threshold for eliciting a MEP is ~ 15% lower when the muscle is contracting (Rothwell *et al.* 1987). The different mechanisms by which TMS and TES excite the corticospinal pathway provide the opportunity to identify the relative importance of changes in corticospinal neuron or spinal motoneuron excitability in this phenomenon, by comparing the extent of contraction-induced facilitation of the MEPs using the two techniques. Involvement of corticospinal neurons in the voluntary contraction of muscle should result in greater MEP facilitation using TMS compared with TES. This view is supported by the finding that tonic voluntary contraction of a target muscle decreases the threshold for indirect activation of corticospinal neurons but not for direct activation of their axons (Mazzocchio *et al.* 1994).

In the present study I found that the contraction-induced facilitation of the MEP was larger using TMS than TES in 12 of 14 comparisons (Fig. 6.3). The contraction-induced facilitation of MEPs in FDI was significantly larger using TMS than TES when the non-dominant hand was used for the task, but not when the dominant hand was used (Figs. 6.2, 6.3). The MEP facilitation at each force level using TES was very similar in each hand, suggesting no differences in spinal alpha motoneuron excitability between hands. I

interpret these findings as indicating that increased corticospinal neuron activity contributes to the contraction-induced facilitation of the MEP in FDI using TMS (see below), but to a much greater extent when the non-dominant hand is used for the task. The relative difference in MEP facilitation with the two techniques was greater for weak contractions, and reduced at high forces. This is consistent with evidence that corticospinal neurons controlling finger muscles are less active in power tasks, compared with precision tasks (Muir & Lemon, 1983). There is also indirect evidence in humans that the relative contribution of corticospinal neurons to the net excitatory drive to motoneurons decreases in more forceful contractions. Brouwer *et al.* (1989) analysed the increase in discharge probability in nine MUs from FDI or tibialis anterior at the fast corticospinal latency following TMS while they discharged at two different mean rates (about 6 Hz and 11 Hz, on average). They found that TMS was less effective when the units discharged at the higher rate (this would be accompanied by slightly higher whole-muscle forces). They interpreted their findings as indicating that corticospinal neurons were less active during sustained isometric contractions at higher forces. One caveat is that stimulus strengths used by Brouwer *et al.* (1989) were much weaker (just sufficient to activate the lowest threshold MUs in active muscle) than those used in the present study, and a much smaller range of voluntary activation levels were examined.

Hess *et al.* (1987) compared contraction-induced facilitation of MEPs in abductor digiti minimi of the right hand using TMS and TES, and reported that the mean MEP amplitude was about 40% larger with TMS for voluntary contractions of 5-10% of maximal. This force range (5-10% of maximal) was the range (2 and 3.5N) in which the largest differences were evident in MEP amplitudes produced by TMS and TES in the present study. My findings in the right hand were similar to those of Hess *et al.* (1987). The MEP in the right FDI was 46% and 32% larger with TMS for the 2N and 3.5N contractions, respectively (Fig. 6.3). The difference between the two techniques was much greater, however, in the FDI of the non-dominant hand at the same force levels (2N, 185%; 3.5N, 184%).

These findings are in some conflict with two previous studies that compared contraction-

induced facilitation of MEPs produced by TMS and TES, and found little evidence for a role of corticospinal neuron excitability changes in the contraction-induced facilitation of the MEP (Maertens de Noordhout *et al.* 1992; Ugawa *et al.* 1995). Maertens de Noordhout *et al.* (1992) compared the contraction-induced facilitation of MEPs in TA muscle using three techniques (TMS, TES, and cervical electrical stimulation). These authors found a comparable degree of facilitation with each technique, and concluded that increases in spinal excitability had the greatest effect on the facilitation of the MEP with voluntary activation. However, for activation of leg muscles, both TMS and TES appear to primarily activate corticospinal neurons directly (Priori *et al.* 1993) and this may be why facilitation of the MEP was similar with the two techniques. Apart from this methodological limitation, the conclusions of Maertens de Noordhout *et al.* (1992) are in keeping with anatomical (Kuypers, 1981) and electrophysiological (Clough *et al.* 1968; Jankowska *et al.* 1975) evidence which suggests that the fast-conducting, direct corticospinal pathway is less effective in activating the lower leg muscles compared with the intrinsic hand muscles. Sustained tonic activation of TA may well be achieved largely by activation of less direct pathways not amenable to study with TMS, such as the corticoreticulospinal pathway. Ugawa *et al.* (1995) examined contraction-induced MEP facilitation using the right FDI muscle in subjects whose hand preference was not stated. Ugawa *et al.* (1995) standardised stimulus strengths for TMS, TES and electrical stimulation at foramen magnum level under conditions of weak voluntary activation, whereas in the present study stimuli were standardised at passive threshold. The latter approach allows the increase in corticospinal neuron activity associated with the transition from passive to active contraction to contribute to the differences in MEP facilitation with the two techniques, and should enhance the differences between TMS and TES in the extent of facilitation of MEPs under active conditions. Ugawa *et al.* (1995) found a similar extent of facilitation for TMS and TES at 10% and 25% MVC, and a larger MEP with TMS at 50% MVC. As the subjects were probably mostly RH, these findings for the dominant hand at low forces are in agreement with those of the present study. The finding of larger MEP facilitation with TMS at the 50% contraction level by Ugawa *et al.* (1995) was not observed in the present study, and is

difficult to reconcile with evidence that corticospinal neurons are less active in power tasks compared with precision tasks (Muir & Lemon, 1983). Ugawa *et al.* (1995) normalised the MEPs with respect to the size of MEPs obtained with weak stimuli during minimal voluntary contraction. A normalisation procedure using minimal MEPs, which are somewhat variable as well as very small, could lead to quite large effects on the magnitude of the normalised MEP, and may have influenced their results.

6.4.2 Hemispheric differences in corticospinal excitability

The main finding in the present study was that the contraction-induced facilitation of the MEP in FDI was significantly larger when the non-dominant hand was used for index finger abduction, but only with TMS and not TES. It follows that the size or effectiveness of the corticospinal volley evoked by TMS to the non-dominant hand was larger than that to the dominant hand under these equivalent stimulus conditions (relative to passive threshold) and levels of voluntary activation.

Before interpreting these differences in terms of differences in activity of corticospinal neurons in the two hemispheres, it is necessary to exclude the possibility that the potential for corticospinal involvement in voluntary movement or activation by TMS is biased in favour of the non-dominant hand. That is, the corticospinal pathway directed to the non-dominant FDI could be greater in extent (more corticospinal axons), or effectiveness (larger EPSPs produced in motoneurons), or more effectively excited by TMS (differences in number, efficacy or activity of excitatory and inhibitory inputs to corticospinal neurons that are activated by TMS). These possibilities seem unlikely for several reasons. There are more corticospinal tract axons directed to the right side of the body than the left in most human brains (Yakovlev & Rakic, 1966; Nathan *et al.* 1990), a finding that is apparently unrelated to hand preference (Kertesz & Geschwind, 1971). It is not known however if the fast corticospinal fibres (responsible for the MEP), which comprise only a small proportion of corticospinal axons, are uniformly distributed to both sides of the body. Using intracortical microstimulation in the anaesthetised squirrel monkey, Nudo *et al.* (1992) found that distal forelimb representations in motor cortex were greater in number and larger

in total area in the hemisphere controlling the preferred hand. In the resting state in man, the hemisphere controlling the dominant hand has the lower (between 2-6% of stimulator output) threshold for TMS activation of small hand muscles (Macdonell *et al.* 1991; Triggs *et al.* 1994) and the larger cortical representation of the target muscle (Wassermann *et al.* 1992). In the present study, passive threshold for TMS was about 2% lower on average for the hemisphere controlling the dominant hand, but the differences were not statistically significant, presumably due to the smaller sample size (8 subjects compared with 19 and 60 in the previous studies). The anatomical evidence and neurophysiological findings in the resting and anaesthetised states suggest that corticospinal inputs to hand muscles should be more effective in the dominant hand, rather than the non-dominant hand.

In view of the preceding arguments, the most likely explanation for the differences in facilitation of the MEP that was observed in each hand with voluntary activation of FDI is that corticospinal neurons controlling FDI that were activated by TMS were more active when the non-dominant hand was used to perform the task. There is some evidence for hemispheric asymmetry in activation of the fingers in man. Measurements of cerebral blood flow in RH humans reveal a greater increase in flow in the Rolandic region of the right hemisphere during finger movements of the left hand than vice versa (Halsey *et al.* 1979). If these cerebral blood flow differences represent increased discharge in right hemisphere corticospinal neurons, or cortical interneurons which excite them, they would support the present findings. Using magnetoencephalography, however, Volkmann *et al.* (1996) found a greater motor cortex area of activation in the hemisphere controlling the dominant hand compared to the same task with the non-dominant hand in RH subjects. Unfortunately with both of these techniques the cortical neurons responsible for the increased activity cannot be identified, so it is not possible to directly relate these observations to the present conclusions regarding hemispheric asymmetry in corticospinal neuron activity.

There is some evidence for lateral differences in H reflexes of wrist (Tan, 1989a) and thumb (Tan, 1989b) flexor muscles that are related to hand preference. Maximal amplitude of H reflexes, H-reflex recovery curves, and facilitation of the H reflex with voluntary activation

were all reported to be larger in the preferred hand. Similarities in MEP facilitation in each hand using TES in the present study argues against an asymmetry of alpha motoneuron excitability, and the H-reflex data may reflect lateral differences in tonic pre-synaptic inhibition of the Ia afferent synapse with motoneurons of the target muscle under resting and active conditions. Lateral differences in activity of the descending pathways, which are known to modulate levels of presynaptic inhibition in a number of reflex pathways (see Rudomin, 1990), may contribute to these differences. Alternatively, it has previously been argued that there is a greater ability of fractionated movement of the intrinsic hand muscles which control the digits (such as in FDI) compared to the wrist muscles (Chapter 2). As the CM cells are important for this fine control, there may be differences in the organisation or effectiveness of the corticospinal projections between the intrinsic hand muscles and muscles controlling wrist movement. It is possible that these differences may result in greater corticospinal facilitation in the muscle controlling the wrist, but less corticospinal facilitation to intrinsic hand muscles during a simple task such as index finger abduction.

An important issue is whether the lateral differences in contraction-induced facilitation of MEPs that has been demonstrated are mediated by the CM component of the corticospinal tract, or by corticospinal action on segmental interneurons. I have recently shown that MU short-term synchronization in FDI is greater in the non-dominant hand of RH subjects than in the dominant hand (Chapter 2). Short-term synchronization (a tendency of neurons to discharge within a few milliseconds of each other that is slightly greater than expected by chance) is a prominent feature of the discharge of MUs in the hand muscles, and is believed to arise by the simultaneous generation of EPSPs in the motoneurons by activity in shared branched-axon collaterals from single last-order neurons (Sears & Stagg, 1976; Datta & Stephens, 1990). The corticospinal pathway is likely to be important in the generation of MU short-term synchronization in man (Farmer *et al.* 1990; Datta *et al.* 1991; Farmer *et al.* 1993b), presumably via monosynaptic projections which are known to project widely within the motoneuron pool from single CM cells (Mantel & Lemon, 1987). Task-related differences have been noted in MU synchrony (Bremner *et al.* 1991c) as well as MEP amplitude using TMS (Datta *et al.* 1989; Flament *et al.* 1993; Schieppati *et al.* 1996).

Surprisingly, however, TMS is not very effective at synchronizing the discharge of concurrently active MUs (Mills & Schubert, 1995). These results suggest that the large composite EPSP following TMS results from the synchronous activation of fast CM cells which are not widely divergent within the motoneuron pool. This raises the possibility that there may be a separate subset of CM cells which are divergent enough to produce MU short-term synchronization, but are not activated by TMS. Although it is unknown how this might occur, the present data suggest a link between the excitability of the corticospinal neurons which are activated by TMS and the common stem presynaptic inputs responsible for MU short-term synchronization during a similar task. In the pooled data, the difference between hands in MU synchrony and MEP facilitation with TMS were in the same direction and of similar magnitude for similar conditions of activation of FDI. For the four subjects who contributed to both studies, the relationship between these two variables was strong (Fig. 6.4, $r^2 = 0.9$). As CM inputs are important for MU synchrony, differences in activity of CM cells seems likely to be an important contributor to the results obtained with TMS.

It is tempting to speculate that lateral differences in corticospinal activity during the task are related to the preferential use of the dominant hand for fine motor tasks requiring skilled control. It is well established that the corticospinal tract is the neuronal substrate for independent activation of muscles moving the digits (see section 1.3.3), and that this pathway is essential for the skilled use of the fingers in tasks such as writing, grasping objects between thumb and index finger, or fastening buttons. The details of the specific role of the corticospinal projections in skilled finger movements are still under investigation, and it is not known how their activation patterns are altered as motor skill is honed by training, or as tasks become automated by practice. The CNS has the capacity to change the balance of the descending command between direct and indirect pathways depending on the requirements of the task. Direct recording of neurons in motor cortex provides several examples of corticospinal neurons that are more active in tasks requiring precise voluntary control of muscle activation (Cheney & Fetz, 1980; Muir & Lemon, 1983). Simplistically, one might expect that the dominant hand would accomplish its more skilled performance in everyday tasks by a relatively stronger descending influence from corticospinal neurons.

This apparently is not the case for a simple tonic isometric contraction of FDI (even though the task calls for its activation in isolation), as both the MU synchrony and TMS data suggest that this task is accomplished with less activity in CM cells when performed with the dominant (skilled) hand than with the non-dominant hand. The corollary is that indirect descending pathways contribute relatively more to this task when it is performed with the dominant hand. It is interesting that one subject showed the opposite pattern; perhaps coincidentally he also had the lowest laterality quotient (0.5) in this group of right-handers. The extent of corticospinal activation used to perform the task may well be more closely related to aspects of skilled task performance, such as the accuracy of force-matching, rather than simply the stated hand preference. This should be examined in future studies. The index finger abduction task was very simple to perform, and it would be interesting to investigate whether a more demanding task performed with dominant and non-dominant hands might reveal a different pattern of corticospinal neuron activity in the two hemispheres, and what if any is the relationship between this pattern and task performance.

In summary, results obtained with two independent techniques (analysis of MU synchronization and transcranial brain stimulation), point to a reduced involvement of corticospinal neurons in the descending command controlling FDI when the dominant hand is used to perform simple index finger abduction. It remains to be seen whether these differences in corticospinal function may be related to differences in the ability to use the hand that are associated with a lifetime of preferred use of the dominant hand for fine motor tasks.

CHAPTER 7

CONCLUDING REMARKS AND CONCLUSIONS

This thesis has been concerned with the influence of different muscle usage patterns on control properties of human motor units (MUs) and their effects on tremor force fluctuations. Due to its importance in the control of finger movements, particular emphasis has been placed on the corticospinal pathway, by examining MU short-term synchronization and muscle-evoked responses to brain stimulation (both of which may provide some information on the activity in corticospinal pathways) in hands which have been utilised for different tasks. As the activity of corticospinal neurons underlies fine control of individual digits, it is reasonable to assume that the operation of this pathway may be altered by different muscle usage patterns, or by different training regimes. The issues examined in the present series of experiments fall into three broad areas of investigation: (1) to examine the control differences in individuals who have trained their hands for different muscle usage patterns; (2) to determine whether control differences in hands trained for various tasks contribute to differences in the precision of force production (force tremor); and (3) to determine whether the discharge patterns of MUs in different subjects influences the precision of force production.

Discharge patterns of single MUs (mean interspike intervals (ISIs) and their coefficient of variation) were similar in all subject groups and were not related to MU synchrony or tremor. The only significant difference was in skill-trained subjects, who exhibited a tendency to control their MUs at a slightly faster discharge rate. However, under the present conditions, the MUs in the first dorsal interosseous (FDI) muscle were not specifically trained in isolation. More standardised testing conditions are required before any conclusions can be established regarding systematic variations in the discharge rate of MUs in skilled and unskilled hands.

The extent of MU synchronization was examined in each hand of untrained (right-handed (RH) and left-handed (LH) subjects) and trained (skill- and strength-trained) subjects. The mean strength of MU synchronization was weak, and of equivalent strength in both hands of skill-trained subjects and the dominant (skilled) hand of untrained RH subjects. The stronger FDI MU synchrony in the non-dominant hand of untrained RH subjects was equivalent to that found in both hands of untrained LH subjects, and both hands of strength-trained subjects. Using a second measure of correlated MU discharge (common drive), the extent of common modulation of firing rates was found to be weaker in skill-trained subjects compared to untrained and strength-trained subjects. A reduction in both measures of correlated MU discharge in skill-trained subjects indicate that certain features of the neural control of the FDI motoneuron pool are different in these individuals. Transcranial stimulation was used to examine the operation of the corticospinal pathway in some subjects (see below).

Force tremor was quantified in each hand in the same subjects during isometric index finger abduction at low forces, and directly compared with the extent of MU synchronization within the muscle. Although tremor amplitude was similar in dominant and non-dominant hands of all subject groups, the amplitude of the tremor force fluctuations were much lower in skill-trained subjects. MU synchronization and common drive have the potential to influence the precision of force production, and it is tempting to equate the more independent activation of MUs to the reduced tremor amplitude, as both measures of correlated MU discharge were lower in skill-trained subjects. However, the less synchronous discharge of pairs of FDI MUs in skill-trained subjects was not responsible for their reduced tremor amplitude. Linear regression revealed that MU synchronization and tremor were not related. Long-term use of FDI muscles in skilled tasks is associated with more independent discharge of MUs, but other alterations in neural or peripheral muscular factors are responsible for the reduced tremor in skill-trained subjects. It is unknown whether the reduced synchronization and tremor amplitude in skill-trained subjects results from a genetic predisposition, or is susceptible to modifications following a specific training regimen. The results from this

thesis suggest that an examination of the MU discharge patterns in muscles which undergo a specific training program should be an area of future investigation.

CM cells from the contralateral motor cortex are likely to be important in the production of MU short-term synchronization, and the most probable explanation for reduced MU synchronization in skilled hands is a difference in the properties of the corticospinal input to motoneurons within the FDI motoneuron pool of these hands. Two possibilities exist to explain the reduced MU synchronization observed in MUs of skilled hands: (1) a reduced effectiveness of the synchronizing CM projections to the FDI motoneuron pool, and (2) reduced CM cell activity during the task when it is performed with skilled hands. I have tested the latter hypothesis in the dominant (skilled) and non-dominant (unskilled) hands of untrained RH subjects using transcranial magnetic (TMS) and electrical (TES) stimulation, which activate the corticospinal pathway at different sites. The amplitude of the responses to TMS (but not TES) were significantly influenced by corticomotoneuronal (CM) cell activity. Following TMS, the normalised MEPs in pooled data were larger in the non-dominant hand during FDI muscle activation. The MEPs were facilitated to an equal degree in each hand following TES, suggesting no lateral differences in spinal excitability or strength of corticospinal projections. These findings support the conclusion that simple index finger abduction in RH subjects is accomplished with less activity in corticospinal neurons when it is performed with the dominant (skilled) hand compared with the non-dominant (unskilled) hand.

The hemispheric differences in corticospinal effectiveness following TMS were sufficient to explain the differences in MU synchrony in dominant and non-dominant hands during comparable low-force contractions and were related in individual subjects. This suggests that weaker MU synchrony in the dominant hand of untrained RH subjects reflects a reduced excitability of corticospinal neurons when this hand was used to perform the task. Reduced MU synchrony was evident in both hands of skill-trained subjects, and it remains to be seen whether corticospinal excitability is reduced in both hands of skill-trained subjects when they perform a simple task. An interesting issue to follow up is whether a task requiring more

skilled performance may reveal differences in corticospinal excitability when performed by a skill-trained hand.

In another line of investigation, the strength of MU short-term synchronization and common fluctuations in mean firing rate (common drive) were examined in the same MU pairs, in order to evaluate the importance of shared branched-axon CM inputs to motoneurons in the genesis of common drive. Shared, branched-axon CM inputs are regarded as the principal determinants of MU short-term synchronization. It was unknown to what extent these synaptic inputs are responsible for the common drive behaviour of MUs. Linear regression in the same MU pairs revealed a weak, significant positive correlation between the strength of MU short-term synchronization and the strength of common drive. These data suggest that only a small proportion of the variation in the strength of common drive exhibited by pairs of MUs can be accounted for by differences in the strength of MU short-term synchronization. It was concluded that the widely divergent, branched-axon inputs from single corticospinal neurons which give rise to MU short-term synchronization play only a minor role in the generation of common drive of MU discharge rates.

Finally, the strength of MU synchronization was quantified using the surface electromyogram (EMG) and MU cross-correlation procedures in the same subjects. This was performed for two reasons: (1) one previous report suggested that MU synchronization was greater in weightlifters than control subjects, and the surface EMG method was used in that investigation, and (2) many MUs are required to obtain a reliable estimate of MU synchronization from cross-correlation, and it is unknown whether the simplified surface EMG method provides a reliable, overall impression of MU synchronization by sampling from a small number of reference MUs. The surface EMG technique is a less direct method of estimating MU synchrony, which has some technical limitations. Using the surface EMG technique, there was no difference in the strength of MU synchrony between skill-trained, strength-trained and untrained subjects, despite cross-correlation revealing greater MU synchronization in strength-trained subjects in a population of the same MUs. Also, I found no significant correlation between the mean strength of synchrony in a muscle measured by

the surface EMG and cross-correlation procedures. These results suggest that MU synchronization measured from the two methods are not equivalent, and the surface EMG method does not provide a reliable estimate of MU synchronization that is comparable to the more direct cross-correlation of MU discharge (estimated for a large number of MU pairs). It is likely that methodological problems encountered when using the surface EMG limits the usefulness of the technique as an estimate of overall MU synchronization. While my finding using cross-correlation of increased FDI MU synchronization in weightlifters is in agreement with the earlier study using the surface EMG method, direct estimation of MU synchrony (as in the present study) appears to give the more reliable estimate of changes in MU synchrony that may accompany training.

CHAPTER 8

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corticospinal tract: a single-fibre EMG study of individual motor unit responses. *Brain Res.* **422**, 196-199.

CHAPTER 9

APPENDIX A

EDINBURGH HANDEDNESS INVENTORY

Surname..... Given Names.....

Date of Birth..... Sex.....

Please indicate your preferences in the use of hands in the following activities by *putting + in the appropriate column.* Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, *put* + +. If in any case you are really indifferent *put + in both columns.*

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all of the questions, and only leave a blank if you have no experience at all of the object or task.

		LEFT	RIGHT
1.	Writing		
2.	Drawing		
3.	Throwing		
4.	Scissors		
5.	Toothbrush		
6.	Knife (without fork)		
7.	Spoon		
8.	Broom (upper hand)		
9.	Striking Match (match)		
10.	Opening box (lid)		
i.	Which foot do you prefer to kick with?		
ii.	Which eye do you use when using only one?		

L.Q. value* = ...

* the LQ value is the total number of +'s for the RIGHT hand boxes, less the total number of +'s for the left hand boxes, divided by the total +'s in both RIGHT and LEFT hand boxes.

APPENDIX B

CURRICULUM VITAE

NAME John Gregory SEMMLER

PRESENT POSITION Research Officer, Dept. of Medicine, The University of Adelaide and Royal Adelaide Hospital.

PERSONAL

Date/Place of Birth: February 2, 1971, Australia

Citizenship: Australian

Family Status: Married to Jayne, no children

Phone: (08) 222-5247 (W)

(08) 362-6405 (H)

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Email: JSEMMLER@medicine.adelaide.edu.au

ADDRESS

Work: Dept. of Medicine, Royal Adelaide Hospital, Nth Terrace, Adelaide 5000, Australia.

Home: 1/134 First Ave. Joslin, Adelaide 5070, Australia.

EDUCATION

University of South Australia, Adelaide, Australia	B.App.Sc.	1991
University of Adelaide, Adelaide, Australia Department of Physiology Dissertation Title: Estimation of synaptic potentials in tibialis anterior motoneurones in humans Honours supervisor: Dr. Kemal S. Türker	B.Sc.(Hons.I)	1992
University of Adelaide, Adelaide, Australia Department of Physiology Dissertation Title: Effect of training on corticospinal control of human motor units Ph.D. supervisor: Dr. Michael A. Nordstrom	Ph.D.	submitted November, 1996

PROFESSIONAL EXPERIENCE

University of Adelaide, Adelaide, Australia Department of Physiology	Teaching Assistant	1993-present
Royal Adelaide Hospital, Adelaide, Australia Department of Medicine	Research Officer	July, 1996-present

MAJOR FIELDS OF RESEARCH

Experiments in humans:

A Mechanical and control properties of single motor units in human limb muscles during voluntary isometric contractions. Features include:

1. Quantitative reflex testing using single motor units (mainly the segmental effects of muscle spindle Ia afferents),

2. The effects of muscle usage patterns (hand dominance, strength *vs.* skill training) on discharge properties of voluntarily activated single motor units and physiological hand tremor,
3. The effects of fatigue on discharge properties of single motor units and physiological tremor.
4. Examination of hemispheric differences in motor cortex excitability during muscle activation.

***B** Neurophysiology of movement disorders in human disease. Features include:*
1. Examination of movement control in Parkinsons Disease patients following pallidotomy,
2. Resetting of tremor with magnetic brain stimulation in patients with orthostatic tremor,
3. Neurophysiological examination in a patient with propriospinal myoclonus.

Particular methods involve:

1. The collection and assessment of single motor units to observe the firing rate interactions between motor units (motor unit synchronization and common drive).
2. The use of Fast Fourier Transforms for frequency power spectral analysis of force signals for physiological tremor measurement and identification.
3. The use of transcranial magnetic and electrical stimulation to evaluate the operation and integrity of the corticospinal pathway during muscle activation,
4. The use of transcranial magnetic stimulation to determine the origin of tremor production in orthostatic tremor.

TEACHING EXPERIENCE

(5 lectures, 83 tutorials, 113 research project practicals)

University of Adelaide, Adelaide

Medicine IIMB Topic: Respiratory Physiology (12 tutorials, 26 pracs)	second year medical students 16-20/class	1993
Medicine IIMB Topic: Cardiovascular Physiology (6 tutorials, 13 pracs)	second year medical students 17/class	1994
M.Sc. in Exercise Physiology Topic: Interlimb effects on strength imagined contraction training (2 tutorials)	Exercise physiology masters students 3-4/class	1994,95
Neurobiology III Topic: Neurophysiology reflexes, psychophysics (52 tutorials, 61 pracs)	final year science students 17-25/class	1994,95,96
Physiology II Topic: Neuromuscular Physiology (13 pracs)	second year science students 22/class	1996
Human movement III Topics: central fatigue neural adaptations to training (2 lectures)	final year science students 90/class	1996
M.Sc. in Exercise Physiology Topics: proprioception neural adaptation to training (11 tutorials)	Exercise physiology masters students 3/class	1996

University of South Australia, Adelaide

Exercise Physiology 1G Topics: neural control of force fatigue, training (2 lectures)	postgraduate physiotherapy students 12-18/class	1993,95

Normal Neuromuscular Control Topics: motor control, fatigue (1 lecture)	Distance Education System Lecture Video package for physiotherapists	1994

HONOURS AND AWARDS

Outstanding Academic Achievement Award — 1991
(Award for outstanding academic achievement (top of class) in Bachelor of Applied Science for Exercise and Sport Science)

University of Adelaide, 1st class Honours — 1992
(Awarded 1st class honours for studies in B.Sc. (Hons.) degree in neurophysiology in the Department of Physiology)

University of Adelaide Scholarship (UAS) — 1993-96
(Award to provide financial support for postgraduate research during study towards a doctorate at the University of Adelaide)

The Australian Federation of University Women Inaugural Diamond Jubilee Bursary — 1995
(Award to provide financial support for postgraduate students to undertake and complete higher degrees and to encourage advanced scholarship and original research)

Bardavcol Science and Technology Award Finalist — 1995
(One of three finalists in the Science and Technology category for the Young Australian of the Year Award)

PRESENTATIONS

Invited presentations at National and International Symposia.

APPS Satellite Workshop on Human Sensorimotor Control — 1995
Sydney, Australia,
Presentation title: Training and the corticospinal tract.

Presentations at National and International meetings.

Australian Physiological and Pharmacological Society
Sydney, Australia, — 1992, 95
Adelaide, Australia, — 1993

Society for Neuroscience
San Diego, CA, U.S.A., — 1995

Australian Neuroscience Society
Adelaide, Australia — 1996
Title: Influence of muscle usage patterns on motor unit synchronization and force tremor in skill- and strength-trained subjects

Seminars at Universities and Research Institutions in Australia.

Department of Physiology, University of Adelaide
H-reflex: A Review — 1992
The Physiological Adaptations to Weightlessness — 1992
Estimation of Synaptic Potentials in Tibialis Anterior Motoneurones in Humans — 1992
Influence of handedness on motor unit discharge properties and force tremor — 1994
Motor unit synchronization and force tremor in skill- and strength-trained subjects — 1995

TRAVEL GRANTS

From the Australian Physiological and Pharmacological Society to attend the APPS meetings in Sydney, Australia — 1992,95

MEMBERSHIP OF SOCIETIES AND CLUBS

Australian Physiological and Pharmacological Society
Australian Neuroscience Society
Adelaide Motor Control Colloquium

OTHER PROFESSIONAL ACTIVITIES AND RECOGNITIONS

Guest convener of the Adelaide Motor Control Colloquium — 1995

PUBLICATIONS

A. MANUSCRIPTS PUBLISHED IN REFEREED JOURNALS

A1. SEMMLER, J.G. & TÜRKER, K.S. (1994). Compound group I excitatory input is differentially distributed to motoneurones of the human tibialis anterior. ***Neurosci. Lett.*** 178: 206-210.

A2 SEMMLER, J.G. & NORDSTROM, M.A. (1995). Influence of handedness on motor unit discharge properties and force tremor. ***Exp. Brain Res.*** 104: 115-125.

A3. SEMMLER, J.G. & NORDSTROM, M.A. (1997). Motor unit discharge and force tremor in skill- and strength-trained individuals. ***(submitted)***

A4. SEMMLER, J.G., NORDSTROM, M.A. & WALLACE, C.J. (1997). Relationship between motor unit short-term synchronization and common drive in human first dorsal interosseous muscle. ***(submitted)***

A5. SEMMLER, J.G. & NORDSTROM, M.A. (1997). Hemispheric differences in motor cortex excitability during a simple index finger abduction task in man. ***(submitted)***

A6. TSAI, C.H., SEMMLER, J.G., KIMBER, T.E., THICKBROOM, G. STELL, R., MASTAGLIA, F.L. & THOMPSON, P.D. (1997). Modulation of primary orthostatic tremor by magnetic stimulation over the motor cortex. *(submitted)*

In preparation (draft available)

A7. SEMMLER, J.G. & NORDSTROM, M.A. (1996). The surface electromyography and cross-correlation techniques are not equivalent estimates of MU synchronization.

B. PUBLISHED ABSTRACTS AND SHORT COMMUNICATIONS

B1. SEMMLER, J.G. & TÜRKER, K.S. (1992). Estimation of synaptic potentials in tibialis anterior motoneurones in man. ***Proc. Aust. Physiol. Pharmacol. Soc.*** 23:231P

B2. TÜRKER, K.S. & SEMMLER, J.G. (1993). Estimation of synaptic potentials in tibialis anterior motoneurones in man. ***Proceedings of the thirty second International Union of Physiological Sciences.*** 43-44.

B3. SEMMLER, J.G. & NORDSTROM, M.A. (1993). Handedness and motor unit discharge properties in human first dorsal interosseous. ***Proc. Aust. Physiol. Pharmacol. Soc.*** 25:180P.

B4. NORDSTROM, M.A., SEMMLER, J.G. & MILES, T.S. (1994). Handedness, motor unit discharge properties and force tremor. ***Soc. Neurosci. Abst.*** 20:338.

B5. SEMMLER, J.G. & NORDSTROM, M.A. (1995). Motor unit synchronization in the human first dorsal interosseous muscle is not an important determinant of physiological tremor. ***Proc. Aust. Physiol. Pharmacol. Soc.*** 26: 227P.

B6. SEMMLER, J.G. & NORDSTROM, M.A. (1995). Motor unit synchronization and force tremor are reduced in skill- compared to strength-trained subjects. ***Soc. Neurosci. Abst.*** 21: 1433.

B7. SEMMLER, J.G. & NORDSTROM, M.A. (1996). Influence of muscle usage patterns on motor unit synchronization and force tremor in skill- and strength-trained subjects. ***Proc. Aust. Neurosci. Soc.*** 7: 49.

B8. SEMMLER, J.G., WALLACE, C.J. & NORDSTROM, M.A. (1996). Short-term synchronization and common drive of firing rates are relatively independent properties of motor unit discharge during their voluntary activation. ***Proc. Aust. Neurosci. Soc.*** 7: 196.

B9. NORDSTROM, M.A. & SEMMLER, J.G. (1996). Hemispheric differences in motor cortex excitability during simple index finger abduction performed with dominant and non-dominant hands. ***Proc. Aust. Neurosci. Soc.*** 7: 50.

B10. NORDSTROM, M.A. & SEMMLER, J.G. (1996). Motor cortex excitability during task performance is related to hand preference in man. ***Soc. Neurosci. Abst.*** 22: 658.

APPENDIX C

PUBLISHED PAPERS RESULTING FROM THIS THESIS

Reprints of published papers associated with this thesis are shown overleaf.

Semmler, J.G. and Nordstrom, M.A. (1995). Influence of handedness on motor unit discharge properties and force tremor. *Experimental Brain Research*, 104(1), 115-125.