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NEURAL AND MUSCULAR CONTROL OF THE HUMAN EXTENSOR DIGITORUM MUSCLE

By

Douglas Andrew Keen

A Dissertation submitted to the Faculty of the

GRADUATE INTERDISCIPLINARY PROGRAM IN PHYSIOLOGICAL SCIENCES

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

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and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

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Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

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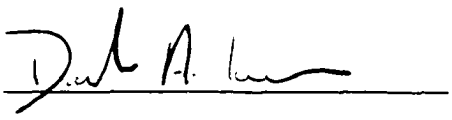
SIGNED: 

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ABSTRACT

The human hand has incredible dexterity which depends, in large part, on the ability to move the fingers relatively independently. Interestingly, many of the primary finger flexor and extensor muscles possess a single belly that gives rise distally to multiple tendons that insert onto all the fingers and consequently might produce movement in all of the fingers. Therefore, the objective of this dissertation was to examine the neuromuscular organization of a multi-tendoned finger extensor muscle, the human extensor digitorum (ED).

Initially, we found that ED spike-triggered average motor unit force was broadly distributed across the digits. Consequently, we hypothesized that linkages between the distal tendons of ED may cause force developed in a single compartment to be transmitted to neighboring tendons. However, force arising from intramuscular stimulation was fairly focused to a single digit suggesting that inter-tendonous connections account for little of the broad distribution of motor unit force.

An alternative possibility was that our spike-triggered averages of motor unit force were contaminated by correlated activity among motor units residing in different compartments. Strong motor unit synchrony was found for motor unit pairs within compartments and a modest degree of synchrony for motor unit pairs in neighboring compartments which likely contributed to the appearance of spike-triggered average motor unit force on multiple fingers. These results suggest that last-order synaptic projections appear to supply predominantly sub-sets of motor neurons innervating

specific finger compartments of ED but also branch to supply motor neurons innervating other compartments.

Finally, single motor axons branch to innervate muscle fibers situated in multiple compartments of ED. Interestingly, force resulting from intraneural microstimulation of single motor axons innervating ED was highly focused to a single digit. Therefore, it appears that the muscle fibers innervated by a motor axon are primarily confined to one of four distinct compartments of ED.

Based on these experiments we believe that each finger is acted upon by ED through a discreet population of motor units. Consequently, extension of an individual finger would require the selective activation of motor neurons innervating a specific compartment of ED.

CHAPTER 1

INTRODUCTION

Throughout history, humans have relied on the skillful control of the hand and fingers to perform a variety of tasks from the construction of crude tools to performance of intricate surgery. Many of these tasks require individuated finger movements in which one finger moves independently of the surrounding digits. One might predict that individuated finger movements are achieved by the activation of individual muscles specific for a task. However, many of the extrinsic hand muscles responsible for flexion and extension of the fingers are single bellied muscles that give rise distally to multiple tendons. For example, extensor digitorum (ED) the primary finger extensor, is a muscle that gives rise to four tendons that insert on each of the fingers. Given this architecture how is it possible to move a single finger without producing motion of the other fingers?

Current thinking is that multi-tendoned muscles such as ED may be comprised of four functional compartments that each produce force selectively on a single digit and thereby provide independent control of each finger (Fritz et al. 1992). This organization necessitates that individual motor units selectively innervate single compartments and produce force focused to individual fingers. Motor units are the functional quantum by which the neuromuscular system controls muscle force and are comprised of a motor neuron and muscle fibers innervated by that neuron. Therefore, the initial purpose of this dissertation was to determine the degree to which single motor unit force in ED is distributed across the fingers. Surprisingly, the force of motor units in ED, evaluated using spike-triggered averaging, was found to be broadly distributed across the fingers. This finding prompted investigations into the specific factors that contribute to the dispersal of motor unit force in ED across multiple tendons.

Three factors that may play a role in the broad distribution of force in ED were investigated in detail in this dissertation. First, connections between the distal tendons of ED may serve to distribute force from individual muscle compartments across more than one finger. This possibility was tested by electrically stimulating contiguous bundles of muscle fibers in ED and recording the force transmitted to each of the four fingers. Force arising from intramuscular stimulation was significantly more focused on a single digit compared with spike-triggered average motor unit force. This suggests that inter-tendonous connections account for only a modest amount of the broad distribution of force observed in ED.

Another factor that might contribute to the broad distribution of spike-triggered average motor unit force is that motor units within different compartments may have been synchronously active with units used in the averaging procedure. The spike-triggered average force of each finger would thus be comprised of the force of a unit whose temporal discharge was used as a trigger for averaging the force records and that contributed by coincidentally active motor units. Such synchronous activity appears to result from common last order inputs to motor neurons from descending neural pathways (Kirkwood and Sears 1978). Therefore, branching of descending inputs may lead to some degree of synchronous activity among motor units in different compartments of ED when attempting to extend a single finger. This possibility was tested by cross-correlation analysis of the firing times of motor units in different compartments. A modest degree of synchrony was found for motor units between compartments. These results suggest that the descending inputs to a pool of motor neurons supplying one

compartment of ED send collateral branches to motor neurons innervating different compartments and may explain part of the broad distribution of motor unit force.

A third factor underlying the broad distribution of motor unit force is that the motor axons of single motor units may branch extensively to innervate muscle fibers in multiple compartments of ED. This was tested using intraneural microstimulation of single motor axons that innervate ED. The force produced by intraneural stimulation was selectively focused on individual digits. These results indicate that control of each finger by ED is accomplished by a discreet population of motor units. However, an inability to selectively activate discreet populations of motor units innervating a single compartment of ED and distal intertendonous connections may result in slightly coupled finger movements.

CHAPTER 2

LITERATURE REVIEW

I Musculature of the fingers and hand

The human hand has an incredible dexterity that allows it to perform a wide variety of movements utilizing countless numbers of physical configurations. An understanding of how the hand performs such a diverse array of functions requires an examination of the musculature that controls the fingers and hand. The muscles that are responsible for movement of the fingers are both intrinsic and extrinsic to the hand.

Forearm muscles

Finger flexors

The two primary finger flexors are flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP). Both of these muscles are located on the ventral side of the forearm and give rise distally to four tendons which insert into each of the fingers (Figure 1). FDS originates from the medial epicondyle of the humerus, the coronoid process of the ulna and from the radius and is innervated by the median nerve. The four tendons that emanate from FDS pass through the carpal canal and insert on the middle phalanges of digits 2 through 5. When active, FDS causes flexion about the metacarpophalangeal (MCP) and proximal interphalangeal joints. FDP lies deep to FDS and originates from the proximal two thirds of the ulna and the interosseous membrane and is innervated by both the median and ulnar nerves. FDP gives rise to four tendons that pass through the bifurcations in the FDS tendons and insert on the distal phalanges of the four fingers and acts to flex all three phalangeal joints (Kahle et al. 1992).

Finger extensors

The extrinsic finger extensor muscles, extensor digitorum (ED), extensor indicis and

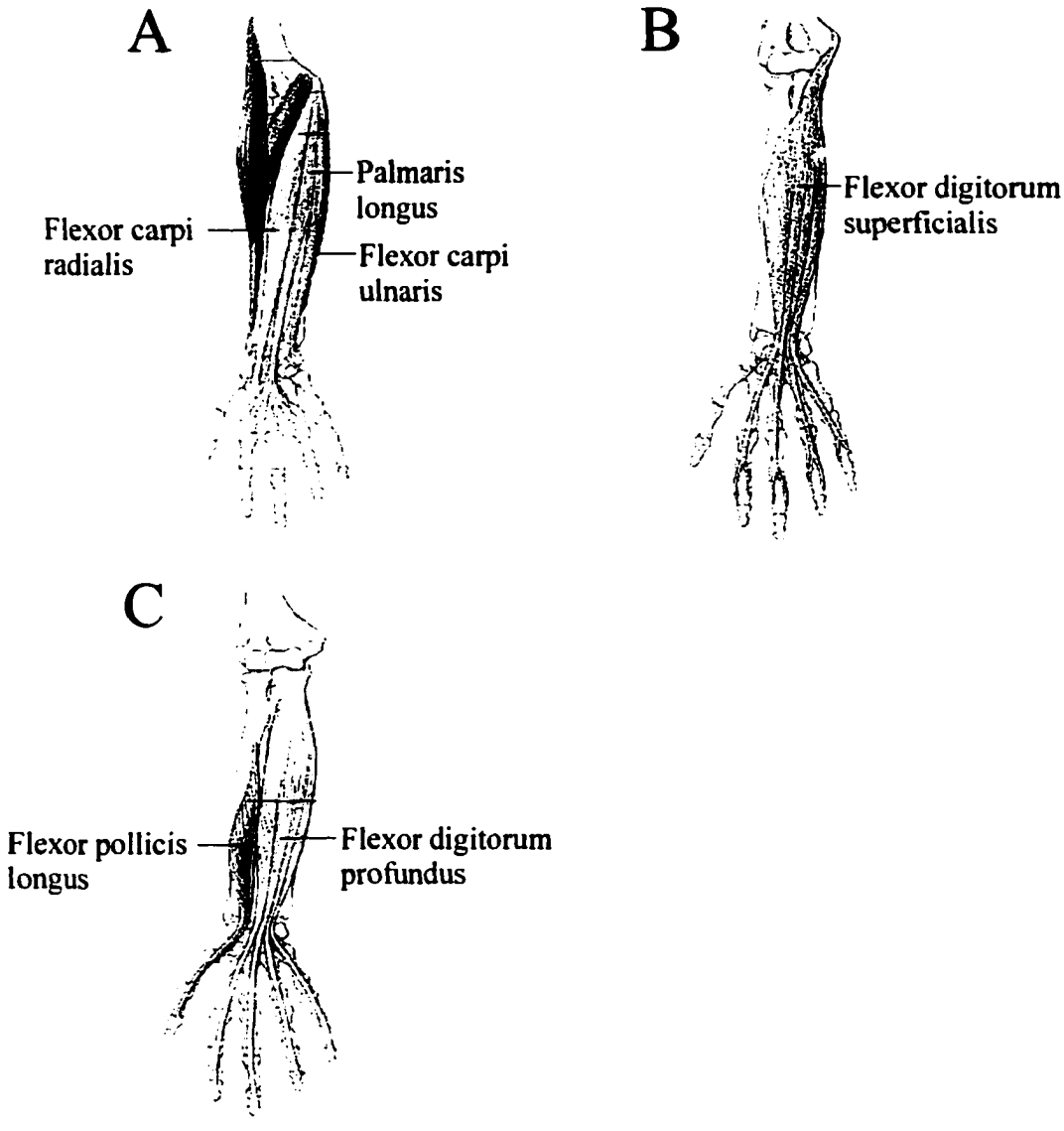

FIGURE 2.1 Three muscle layers of the ventral forearm. The most superficial layer (A), comprises muscles that act on the wrist and include palmaris longus, flexor carpi radialis, and flexor carpi ulnaris. The middle layer (B) consists of a finger flexor muscle, flexor digitorum superficialis, that inserts onto the middle phalanx of each finger. The deep muscle layer (C) is comprised of a thumb and finger flexor, flexor pollicis longus and flexor digitorum, respectively, that insert onto the distal phalanges. (Figure adapted from Agur, 1991)

extensor digiti minimi are all located in the dorsal compartment of the forearm (Figure 2) and are innervated by branches of the deep radial nerve. ED is the most prominent finger extensor and will be the focus of this dissertation. The origin of ED is on the lateral epicondyle of the humerus, the radial collateral ligament, the annular radial ligament and the antebrachial fascia (Kahle et al. 1992). ED gives rise to four tendons distally which are interconnected proximal to the MCP joint by the juncturae tendinium. The juncturae tendinum consist of narrow connective tissue bands extending between the distal tendons of ED and extensor digiti minimi (Figure 2B) (von Schroeder et al. 1990). The tendons of ED insert into the base of the proximal phalanges of the four fingers and continue as the extensor expansion. The extensor expansion is a sheath of connective tissue that covers the dorsum of each finger from the MCP joint to the base of the distal phalanx (Figure 3) and, when engaged, acts to extend both of the interphalangeal joints. Fibers from the extrinsic finger extensors and intrinsic hand muscles contribute to the extensor expansion, which covers approximately two thirds of the circumference of the proximal phalanx. Consequently, activation of ED results in extension of the MCP and both interphalangeal joints. Furthermore, because the tendons of each of the extrinsic finger extensors cross the wrist, when active these muscles also act to extend the wrist (Kaplan and Hunter 1984).

While ED inserts tendons on all four fingers, extensor indicis and extensor digiti minimi have single tendons that act to extend the index and little fingers, respectively. Extensor digiti minimi is a slender muscle located slightly ulnar to ED in the superficial layer of the dorsal forearm (Figure 2B). In fact, extensor digiti minimi shares a common

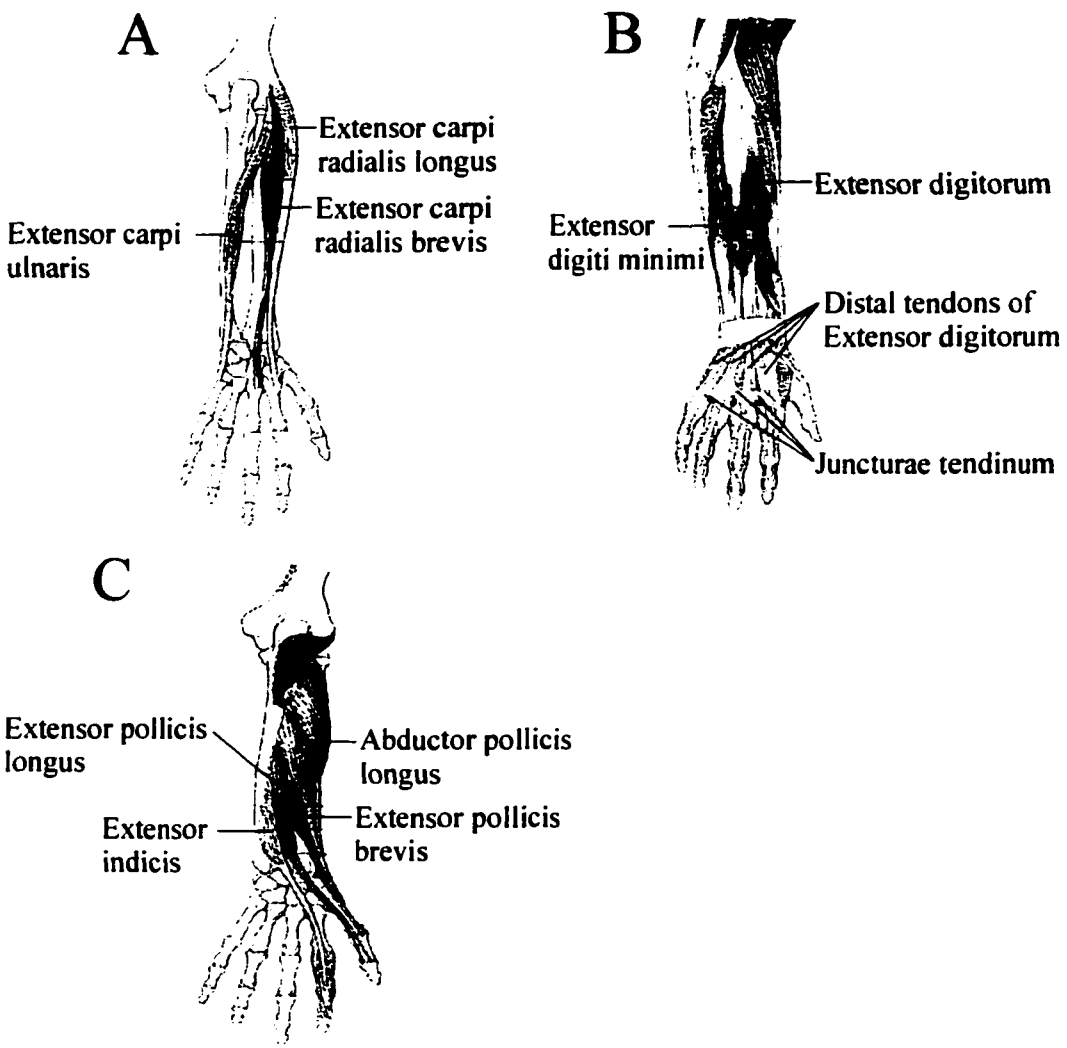

FIGURE 2.2 Muscles of the dorsal forearm. A superficial layer of muscles on the dorsal forearm dedicated to wrist movements (A) is comprised of extensor carpi ulnaris, extensor carpi radialis longus and extensor carpi radialis brevis. The superficial layer also includes the finger extensors extensor digiti minimi and extensor digitorum (B). The four distal tendons of ED and juncturae tendinum that connect these tendons are also shown. Muscles that control the thumb, extensor pollicis longus, abductor pollicis longus, and extensor pollicis brevis and extension of the index finger, extensor indicis, comprise a deeper layer of dorsal forearm muscles (C). (Figure adapted from Agur, 1991)

origin with ED and attaches as two tendons to the extensor expansion of the little finger. The primary action of extensor digiti minimi is to extend the little finger, however, it also acts to extend and abduct the wrist. Extensor indicis is found in the muscle layer below extensor digiti minimi and is a thin muscle in the distal portion of the dorsal forearm (Figure 2C). Extensor indicis originates on the distal third of the ulna and inserts its tendon into the extensor expansion of the index finger and thus acts primarily to extend the index finger and is a weak wrist extensor (Kahle et al. 1992).

Thumb muscles

The human thumb exhibits excellent independent control (Häger-Ross and Schieber 2000) and has four extrinsic single tendoned muscles that are responsible for flexion, extension and abduction of the thumb. Flexor pollicis longus is the only extrinsic thumb muscle located in the ventral forearm and acts to flex the thumb (Figure 1C). Extensor pollicis brevis, extensor pollicis longus, and abductor pollicis longus comprise most of the deep muscular layer of the dorsal forearm (Agur 1991) (Figure 2C). Extension of the thumb is accomplished by the activation of extensor pollicis brevis and extensor pollicis longus, with the most notable difference between these two muscles being the point of insertion on the thumb. Extensor pollicis longus inserts into the base of the distal phalanx of the thumb whereas the tendon from extensor pollicis brevis extends only to the base of the proximal phalanx of the thumb and consequently does not contribute to extension of the distal phalanx. Because the tendons of these two muscles cross the wrist, both of these muscles abduct the hand radially while extensor pollicis longus also causes some extension of the wrist. The primary action of abductor pollicis longus is to abduct the

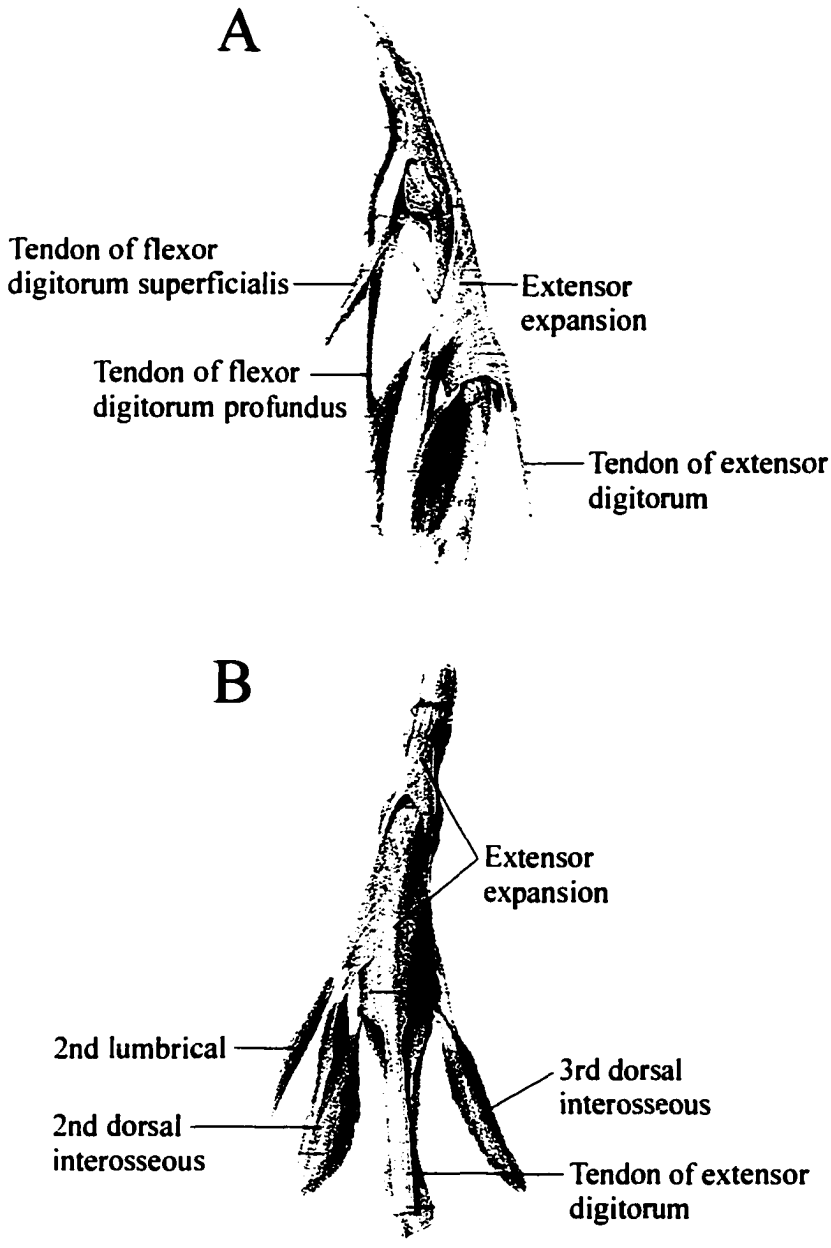

FIGURE 2.3 Side (A) and dorsal (B) view ofthe middle finger extensor expansion. Tendons from the primary finger flexor muscles and extensor digitorum are shown in A. Tendons from the second and third dorsal interossei muscles, second lumbrical, and extensor digitorum contribute to form the extensor expansion (B). (Figure adapted from Agur, 1991)

thumb although it also acts to abduct and flex the wrist. Abductor pollicis longus is unique being the only muscle that is supplied by the radial nerve to contribute to wrist flexion (Brand and Hollister 1999).

Wrist muscles

Movement about the wrist joint is influenced by torque produced by tendons which cross the wrist joint from the extrinsic finger and thumb muscles when they are active (Kaplan and Hunter 1984). However, there are several muscles that are exclusively dedicated to movements of the wrist. Flexor carpi radialis and flexor carpi ulnaris are both muscles in the superficial layer of the ventral forearm (Figure 1A) that act to flex the wrist as well as abduct and adduct the wrist, respectively. Besides flexing and abducting the wrist, flexor carpi radialis also acts as a weak flexor and pronator of the elbow joint. Another muscle in the ventral forearm that acts to flex the wrist by tensing the palmer aponeurosis is palmaris longus. Interestingly, this muscle is absent in approximately 10% of people (Brand and Hollister 1999).

The primary wrist extensors are extensor carpi ulnaris, extensor carpi radialis brevis, and extensor carpi radialis longus (Figure 2A). Extensor carpi ulnaris is a superficial muscle that is found on the mediodorsal side of the ulna. While it is named as an extensor, the primary action of this muscle is wrist abduction. Extensor carpi radialis brevis, and extensor carpi radialis longus are long muscles that span both the elbow joint and the wrist. These muscles have similar actions acting as weak elbow flexors and cause extension and radial abduction of the wrist (Kahle et al. 1992).

While all of the muscles that have been discussed reside in the forearm, it should be acknowledged that several other forearm muscles have not been mentioned. Muscles such as pronator teres and supinator do not have tendons that cross the wrist and therefore have been omitted from this discussion.

Intrinsic Hand Muscles

The Interossei

The plamer and dorsal interossei are a collection of seven short muscles that cause adduction and abduction of the four fingers, respectively (Figure 4). The palmer interossei are three muscles that originate on the second, fourth, and fifth metacarpal bones and insert into the corresponding proximal phalanges and merge with the tendons from ED into the extensor expansion. Their principal action is adduction of the second, fourth and fifth digits with respect to the middle finger. The tendons of the palmer interossei pass anterior to the axis of the MCP joints. Consequently, these muscles also flex the fingers at the MCP joint, yet due to their union with the extensor expansion, they extend the interphalangeal joints (Kahle et al. 1992). The four dorsal interossei, are double-headed muscles that originate from adjacent metacarpal bones. For example, the second dorsal interosseous arises from the second and third metacarpal and causes radial abduction on the middle finger. The insertion of the dorsal interossei is identical to that of the palmer interossei causing both flexion of the MCP joint and extension of the interphalangeal joints. However, the prominent action of the dorsal interossei is the abduction of the fingers (Kahle et al. 1992).

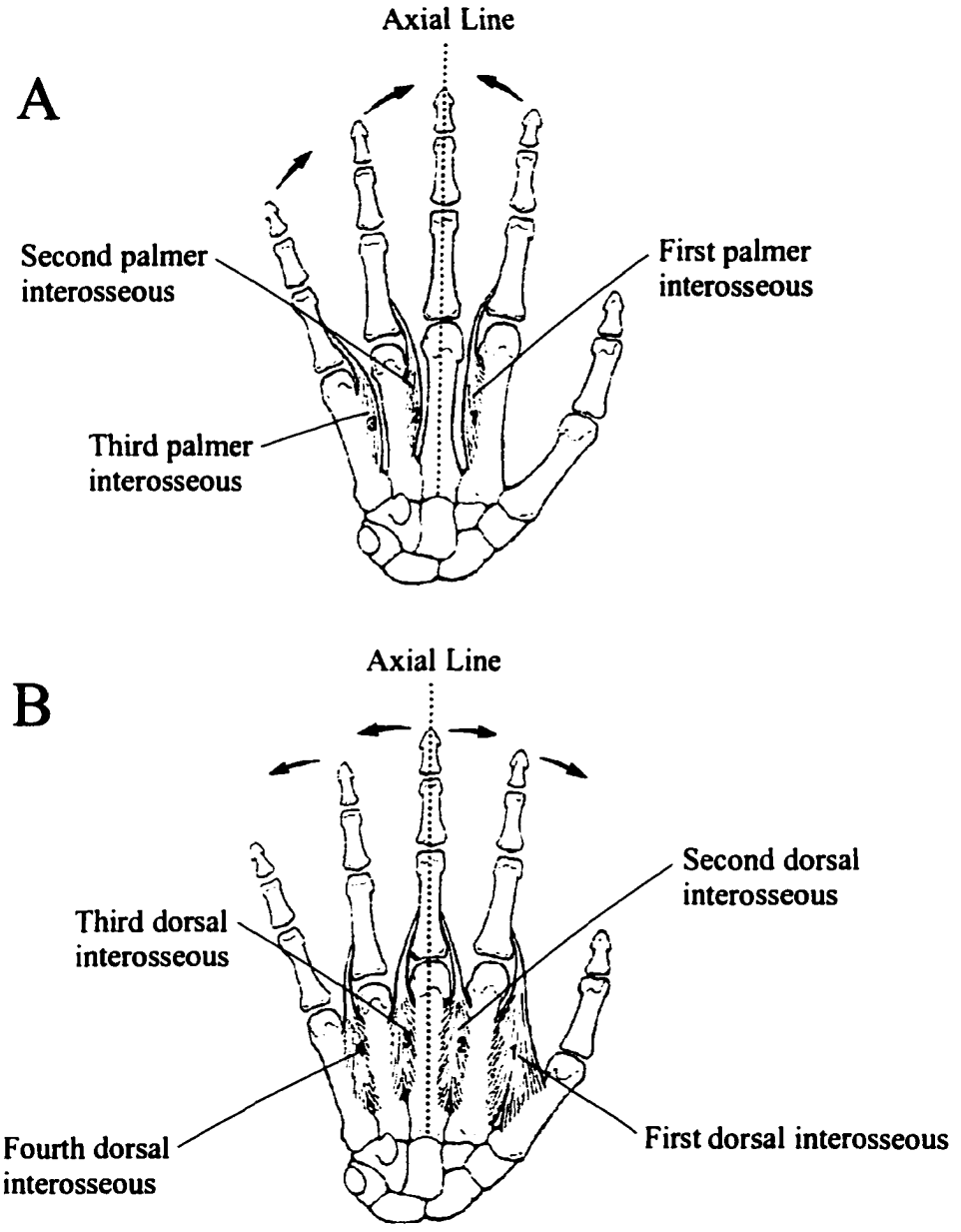

FIGURE 2.4 Interosseous muscles of the hand. The first, second, and third palmer interossei responsible for adduction of D2, D4, and D5 respectively, are shown in A. The first, second, third, and fourth dorsal interossei, which act to abduct D2, D3, and D4 are shown in B. (Figure adapted from Kahle et al. 1992)

The Lumbricals

There are four thin lumbrical muscles comprised of longitudinally running fibers. The two radial lumbricals are innervated by the median nerve and the two ulnar lumbricals are innervated by the ulnar nerve. These muscles are unique in that they originate from the radial sides of the tendons of FDP and radiate into the extensor expansion. The tendons of the lumbricals pass anterior to the MCP joint and ultimately join the extensor expansion resulting in flexion at the MCP joint and extension at the interphalangeal joints when the lumbricals are active. However, the physiological cross-sectional area of the lumbricals is approximately one-tenth that of the dorsal interossei and consequently do not produce much force (Brand and Hollister 1999). Furthermore, it is necessary that tendons of FDP, being the origin of the lumbricals, be taut for the lumbricals to produce torque about any of the phalangeal joints. Consequently, for the lumbricals to have a mechanical effect requires that FDP and the lumbricals be active simultaneously.

The Thenar and Hypothenar Eminences

The thenar eminence is comprised of the abductor pollicis brevis, flexor pollicis brevis, adductor pollicis and opponens pollicis which control the thumb. These muscles are used in abduction, adduction, opposition and reposition of the thumb. Because the actions of these muscles are independent from the focus of the individuation of finger movements, they will not be a focus of this dissertation. While the thumb is one of the five digits of the hand and of critical importance in many of the dexterous tasks the hand performs, for clarity we will not consider it as a finger.

The hypothenar eminence consists of the abductor digiti minimi, flexor digiti minimi brevis, and the opponens digiti minimi muscles. The abductor digiti minimi muscle acts as a pure abductor of the little finger. The action of opponens digiti minimi is to flex and supinate the little finger about the carpometacarpal joint and thus functions to cup the hand. Flexor digiti minimi brevis originates on the hamate of the carpal bone and from the flexor retinaculum and inserts into the palmar surface of the proximal phalanx of the little finger. Consequently, the action of flexor digiti minimi brevis is to flex the little finger about the MCP joint and must be considered when examining flexion movements of the little finger (Kahle et al. 1992).

EMG studies

While the actions of individual extrinsic and intrinsic hand muscles are generally well understood, how these muscles are used during finger movements is unclear. A simplified view is that each digit is moved by its own small set of muscles dedicated for a particular task. For example, extension of the middle finger should require activation of the middle finger compartment of ED. However, the tendons of the extrinsic finger muscles cross multiple joints producing torque about these joints when active. In addition, the force produced by single motor units or neuromuscular compartments in multi-tendoned muscles of the hand may not be confined to a single tendon but exert force on several digits (Schieber et al. 1997; Keen et al. 1998; Schieber et al. 2001). The consequence of such an arrangement is that coactivation of many muscles might occur in order to prevent unwanted movements. Several investigators have recorded the electromyographic (EMG) signal from many hand muscles during various movements of

the fingers in both humans (Long and Brown 1964; Landsmeer and Long 1965; Close and Kidd 1969; Brandell 1970; Long et al. 1970; Rose et al. 1999) and monkeys (Schieber 1993; Schieber 1995). A consistent finding of these studies is that the movement a single finger requires several muscles to be active simultaneously. Some of the activated muscles were agonists and antagonists of the instructed movement while other muscles were active to prevent unwanted movements in neighboring fingers and about the wrist. For example, Rose et al. (1999) reported that during extension of the ring finger, 17 of the 24 muscles recorded in the forearm and hand were active. The muscles that were active included all 4 compartments of ED, several compartments of the extrinsic finger flexors, intrinsic hand muscles and muscles dedicated to the wrist. This high percentage of active muscles for extension of the ring finger was typical for flexion or extension movements of any of the fingers. On average, flexion or extension of a single finger resulted in over 50% of the recorded muscles showing significant activity (Rose et al. 1999). These studies suggest that the coordination of multiple muscles is required to perform movements of an individual finger.

An alternative to coordinating multiple muscles to produce single finger movements is to control these movements using the intrinsic hand muscles. These muscles do not cross the wrist and each finger is equipped with its own dedicated muscles. While EMG studies have found that intrinsic hand muscles are active during flexion and extension of the fingers (Long and Brown 1964; Landsmeer and Long 1965; Long 1968; Close and Kidd 1969; Darling and Cole 1990; Rose et al. 1999), it is generally accepted that this is not their primary role (Schieber 1995). Consistent with these findings is that abduction

and adduction of the fingers are the primary movements evoked by electrical stimulation of the interossei (personal observations). Long et al. (1970) found that during hand closing, the primary muscle used was FDP while the intrinsic hand muscles did not participate. Furthermore, the lumbricals were not active during squeeze grips regardless of the force produced. Thus, only the extrinsic muscles are necessary to produce a fully flexed or a clawed finger configuration (Long 1968).

II The Motor Unit

The preceding section examined the hand musculature at the whole muscle level. However, because the nervous system is responsible for muscle activation, it is necessary to consider the muscle at the level it is engaged by the nervous system. The functional element of the neuromuscular system is the single motor unit, which was originally defined by Sherrington (Liddell and Sherrington 1925) as the motor neuron axon and its adjunct muscle fibers. Subsequently this definition was altered to include the entire motor neuron, its axon and all of the muscle fibers innervated by that axon and is the smallest functional unit by which the nervous system controls force (Burke 1981). The term muscle unit was introduced to define the set of muscle fibers belonging to a single motor unit (Burke 1981).

Intramuscular recordings of the action potentials of single motor units was pioneered by several investigators in the late 1920's (Adrian and Bronk 1929; Denny-Brown 1929). These studies involved the insertion of an electrode into a muscle, which was subsequently activated voluntarily or reflexively. The action potentials of muscle fibers within the detection area of the electrode associated with the discharge of a single motor unit were then recorded. The benefit of this technique is that the discharge of a single motor neuron located in the spinal cord can be measured indirectly. The indirect monitoring of a motor neuron is possible because the efficacy of synaptic transmission at the neuromuscular junction ensures that each action potential of the motor neuron results in an action potential and subsequent contraction of every muscle fiber innervated by that neuron (Paton and Waud 1967). Furthermore, each adult mammalian muscle fiber

receives input from only a single motor neuron, while each motor neuron innervates multiple muscle fibers (Feindel et al. 1952). One of the primary goals of this dissertation is to understand the muscular and neural organization of motor units of ED. This necessitates an examination of the anatomical and neural properties of single motor units.

Anatomy of motor units

The precise number of motor units that comprise human muscles appears to be related to the size and function of the muscle. An increase in muscle size has been shown to be associated with a modest increase in motor unit number (McComas 1991). Using a variety of techniques, the number of motor units in various human muscles has been estimated. For example, several investigators have produced estimates of between 116 to 342 motor units in the thenar muscle group (Stein and Yang 1990; Galea et al. 1991; McComas 1991; Doherty and Brown 1993; Felice 1995). Another intrinsic hand muscle, the first dorsal interosseous, has been estimated to be comprised of approximately 120 motor units (Feinstein et al. 1955). Estimates of motor unit number have not been made in ED. However, several investigators have studied a similar muscle to ED in the foot, extensor digitorum brevis (EDB). The results from these studies estimate mean motor unit numbers of EDB from 143 to 210 motor units (Ballantyne and Hansen 1974; Galea et al. 1991; McComas 1991). Based on these findings from intrinsic hand and foot muscles it is likely that ED is comprised of roughly 200 motor units.

The axons for all of the motor units comprising a muscle as well as afferent and sympathetic nerve fibers are contained within the peripheral nerve. The detailed organization of these fibers within the peripheral nerve is unclear. It is known that in

close proximity to the spinal cord, the peripheral nerve segregates into sensory afferent axons which enter the dorsal root and efferent fibers which enter the peripheral nerve via the ventral root. However, from the spinal cord to the target muscle, different organizations of axons within the peripheral nerve have been described. Hagbarth (1979) reported that axons in the median nerve at the level of the elbow and wrist are segregated into separate fascicles of sensory and motor fibers. Contrary to this view, Westling et al. (1990) reported that in the upper arm that the median nerve contains an average of 10 fascicles which are intermingled with sensory and motor axons. Furthermore, they report that the motor and sensory axons to a given muscle are not contained within one fascicle but are widely distributed amongst the fascicles. This discrepancy may partially be explained by differences in the sites along the median nerve that were studied by the different investigators. However, the organization of motor and sensory fibers within the peripheral nerve is still largely unresolved.

Upon entering the target muscle, the axons of alpha motor neurons branch to innervate multiple muscle fibers. The number of muscle fibers comprising a single motor unit is referred to as the innervation ratio and can vary widely depending on the function of the muscle. For example, extraocular muscles that require precise control have motor neurons that innervate approximately 13 - 20 muscle fibers (Buchthal 1961). Conversely, muscles that are required to produce large amounts of force, such as the gastrocnemius, have been estimated to be comprised of 1,120,000 muscle fibers innervated by approximately 580 motor neurons. Therefore, motor units in the gastrocnemius have a mean innervation ratio of approximately 2000 muscle fibers (Feinstein et al. 1955).

The location of muscle fibers that comprise a single motor unit has been shown using glycogen depletion techniques to be distributed over as much as 30% of the cross-sectional area of a muscle (Burke et al. 1974; Tötösy de Zepetnek et al. 1992a). The details of how muscle fibers of a single motor unit are distributed is of critical importance to this dissertation and will be dealt with in more detail in a later section on neuromuscular compartmentalization.

Motor Unit Contractile Properties

The vast majority of information on the contractile properties of motor units has been derived from non-human animal experiments. These experiments typically involve stimulation of a single motor axon which has been dissected from filaments of cut ventral roots or intracellular stimulation of motor neurons innervating the target muscle. The muscle of interest is connected to a force transducer and the contractile properties of a single motor unit are measured directly in response to stimulation. These types of experiments have yielded fundamental information on the contractile properties of motor units in many muscles of a variety of species from the rat to the monkey (e.g., Close 1967; Eccles et al. 1968; Burke et al. 1973; Kugelberg 1973; Burke et al. 1974; Bagust 1979; Schieber et al. 1997). From these experiments it is clear that motor units comprising a given muscle are rarely found to be homogeneous in their contractile properties but rather differ markedly in their magnitude of force, contraction speed, and susceptibility to fatigue. Nevertheless, motor units have typically been classified into 3 categories based on the latter two of these properties. Type S motor units are slow contracting and extremely fatigue resistant. At the other extreme, type FF motor units are

fast contracting but are very susceptible to fatigue. Type FR motor units share characteristics of both the type S and FF motor units being fast contracting and relatively fatigue resistant (Burke 1981). Differences in the physiological properties of the motor unit types result from systematic anatomical and histochemical variation in muscle fibers comprising the motor unit.

Motor Unit Contractile Properties in Humans

While the techniques of intracellular and ventral root stimulation have been invaluable in illuminating the contractile properties of motor units in animals they cannot be used in humans. Consequently, information on motor unit contractile properties in humans has been indirectly derived using the technique of spike-triggered averaging. This technique extracts the average force impulse of an identified motor unit from the force fluctuations of the whole muscle during a low force voluntary contraction (Milner-Brown et al. 1973c). However, this technique does not allow the force-frequency relation, tetanic force, or standard fatigue test to be assessed. Consequently, intraneural microstimulation of single motor axons in human subjects has evolved as a useful technique to overcome some of the limitations of spike-triggered averaging. Intraneural microstimulation involves the insertion of a tungsten microelectrode into the peripheral nerve and stimulation of a single motor axon at a rate desired by the investigator in a conscious, relaxed human subject. This allows examination of the contractile and force frequency properties of a motor unit to be made by stimulation over a range of frequencies (Bigland-Ritchie et al. 1998). Microstimulation has been used in humans to examine the contractile properties of single muscle units of the thenar (Taylor and

Stephens 1976; Westling et al. 1990; Thomas et al. 1990a), toe extensors (Macefield et al. 1996) and extrinsic finger flexor (Fuglevand et al. 1999) muscles. Interestingly, contraction time in these and other studies did not correlate with other motor unit parameters (Elek et al. 1992; Fuglevand et al. 1999; Mateika et al. 1997; Thomas et al. 1990a) and were therefore not useful in classifying motor unit types, unlike some of the studies performed in cats (Burke et al. 1973). This issue is unresolved and requires further studies of human motor units.

Motor Unit Histochemistry

It has been shown that muscle fibers belonging to a single motor unit have a similar biochemical and histochemical composition (Burke et al. 1973; Nemeth et al. 1986). For example, various myosin heavy chain isoforms have been identified that differ in their specific actin-activated and Ca^{++} dependent myofibrillar actomyosin adenosine triphosphate (mATPase) activity. These differences in mATPase activity have been shown to be a major determinant of contraction speed (Barany 1967; Kugelberg 1973). While several different myosin heavy chain isoforms can be identified in a single muscle, muscle fibers belonging to a single motor unit have a similar isoform and consequently similar mATPase kinetics.

Histochemical and physiological studies have demonstrated that muscle fibers with a long-duration contraction time display high mATPase activity under acidic conditions and low activity under alkaline conditions animals (Burke et al. 1973). Muscle fibers with this profile have been classified as type I fibers and comprise type S motor units. Conversely, muscle fibers with a fast contraction speed exhibit high mATPase activity

under alkaline conditions and low activity under acidic conditions (Pette and Staron 1990). Muscle fibers with this profile have been classified as type II and comprise fast contracting type FR and FF motor units animals (Burke et al. 1973). More detailed studies based on differences in mATPase content have further categorized type II muscle fibers as type II-A or type II-B fibers (Engel 1974). While both subtypes are fast contracting, type II-A fibers are relatively fatigue resistant and generally comprise type FR motor units and type II-B fibers are fatigue sensitive and comprise type FF motor units. Thus, the contraction time of a motor unit is largely determined by the specific mATPase isoform present within the muscle fibers of a motor unit.

Besides contraction time, another property that is used to categorize motor units is their fatigue resistance, which is largely determined by the oxidative and glycolytic enzyme content of the muscle fibers. Three oxidative enzymes that are associated with fatigue resistance are succinate dehydrogenase, and malate dehydrogenase which are enzymes of the citric acid cycle, and B-hydroxylacyl-CoA dehydrogenase which is associated with fatty acid oxidation. Type I and II-A muscle fibers have a relatively high concentration of all three of these enzymes which allows for the aerobic oxidation of substrate and thus confers a strong resistance to fatigue in these fibers. Conversely, muscle fibers of type FF motor units (type II-B) have relatively low concentrations of these oxidative enzymes consequently making them sensitive to fatigue (Burke et al. 1973; Kugelberg and Lindegren 1979; Nemeth et al. 1986). While fatigue sensitive type II-B muscle fibers have relatively low concentrations of oxidative enzymes they have relatively high concentrations of enzymes used in anaerobic metabolism. For example,

adenylokinase which is used for high-energy phosphate metabolism and lactate dehydrogenase which is a marker of anaerobic glycolysis are both found in concentrations four to six times higher in type IIB muscle fibers compared to type I muscle fibers (Nemeth et al. 1986). Therefore, the speed of contraction and fatigue sensitivity of a muscle fiber is dictated by its histochemical and biochemical composition.

Motor Unit Force Capacity

While motor units have been classified based on contraction speed and fatigue resitance, the force produced by motor units in the same muscle can vary by approximately 100 times (Milner-Brown et al. 1973a; Tötösy de Zepetnek 1992b). Motor unit force depends on the product of the total muscle fiber cross-sectional area and the specific tension (force generating capacity per unit of cross-sectional area). In the majority of studies on isolated muscle fibers, the specific tension has been shown to be consistently around 25 N/cm^2 regardless of fiber diameter or type (Lucas et al. 1987; Brooks and Faulkner 1988; Tötösy de Zepetnek et al. 1992b). Therefore, differences in motor unit force are attributed to variability in the total muscle fiber cross-sectional area, which is the product of the innervation ratio and the average cross-sectional area of the individual fibers. To assess the contribution of each of these variables, stimulation of single motor neurons or single motor axons is first done in order to classify motor units based on contractile properties and fatigue sensitivity and to determine maximum force capacity. The motor units are then stimulated for an extensive duration to deplete the fibers of that muscle unit of glycogen. The muscle is then excised and stained for glycogen to enable identification of the stimulated fibers. This technique allows the

number of muscle fibers that belong to a single muscle unit to be counted and the fiber cross-sectional area to be measured.

The average cross-sectional area of the muscle fibers in hind limb musculature of the cat and rat is consistently 2 to 3 times larger in type FF motor units compared with type S motor units (McDonagh et al. 1980; Kanda and Hashizume 1992). Type FR motor units have an intermediate size fiber diameter (Burke and Tsairis 1973; McDonagh et al. 1980; Kanda and Hashizume 1992; Tötösy de Zepetnek et al. 1992a). However, data from muscle biopsy studies in humans have shown that there is not much difference in muscle fiber diameters across fiber types (Tesch and Karlsson 1985; Henriksson-Larsen 1985; Henriksson-Larsen et al. 1985). Therefore, while differences in muscle fiber diameter may account for some of the difference in motor unit force, the most important determinant appears to be the innervation ratio (Bodine et al. 1987; Chamberlain and Lewis 1989; Kanda and Hashizume 1992). For example, Kanda and Hashizume (1992) have shown a nine-fold range of innervation ratio for type S units (~ 40 fibers) compared to type FF units (~360 fibers) in the rat medial gastrocnemius with only a two fold variation in average fiber diameter. Consequently, type S motor units produce the least force and type FF units produce the most force, primarily because of differences in the innervation ratio.

Neural Control

Muscle force during a voluntary contraction may vary considerably. It is the responsibility of the nervous system to activate an appropriate number of motor units, of the few hundred that compose each muscle, to produce a desired force. To achieve this

goal the nervous system uses two mechanisms. One of these is the orderly recruitment of motor units from the weakest to the strongest. The other mechanism involves varying the discharge rate of recruited motor units. These processes of recruitment and rate coding are not mutually exclusive but are utilized concurrently during voluntary contractions to produce a desired amount of force (Adrian and Bronk 1929; Milner-Brown et al. 1973b; Monster and Chan 1977).

The Size Principle

A significant advance in motor unit physiology was made by Denny-Brown and Pennybacker (1938) when they observed that mammalian motor units were recruited in a fixed sequence from weakest to strongest. This finding has proven to be extremely robust with few exceptions and has been termed 'orderly recruitment'. Likewise, experiments on the cat in the late 1950's and 1960's demonstrated that the recruitment of motor neurons appeared to progress from the smallest motor neurons to the largest motor neurons (Henneman et al. 1965a; Henneman et al. 1965b). Subsequently, it was shown in the cat that small motor neurons have a greater input resistance than large motor neurons (Burke et al. 1982). Therefore, in accordance with Ohm's law, smaller neurons will experience a greater change in membrane potential for a given level of synaptic current. Consequently, smaller neurons will reach threshold and discharge action potentials before larger neurons if all neurons receive the same synaptic current. This is contingent, however, on motor neurons having a similar resting membrane potential and threshold voltage, which appears to be the case (Henneman and Mendell, 1981). Therefore, Henneman and colleagues postulated that the size of the motor neuron was a critical

factor in determining the recruitment order. Furthermore, there is also a strong positive correlation between soma size and axon diameter (Cullheim 1978). The significance of an increase in axon diameter is that the axon may branch more extensively to contact a greater number of post-synaptic cells (Eccles and Sherrington 1939). In the case of a motor neuron, this means that there is a direct correlation between soma size and innervation ratio. Therefore, because innervation ratio plays a critical role in determining the force of a motor unit (Bodine et al. 1987; Chamberlain and Lewis 1989; Kanda and Hashizume 1992), larger motor neurons will supply muscle units that produce greater force. Consequently, 'Henneman's size Principle' states that motor neurons are recruited in an orderly manner from those with the smallest cell bodies to those with the largest so that recruitment generally proceeds from the weakest to the strongest units. It is recognized that other properties both intrinsic and extrinsic to the motor neuron may also influence the recruitment threshold of motor neurons. For example, differences in membrane resistivity (an intrinsic property) could effect the orderly recruitment of motor neurons independent of cell size (Gustafsson and Pinter 1985). Alternatively, extrinsic factors such as differences in the density of the synaptic input onto the motor neurons may influence the recruitment threshold of a motor neuron (Burke 1968).

Input Distribution

Besides cell size, the distribution of synaptic input onto the motor neurons can also influence recruitment order. For example, small neurons have been shown to receive a greater synaptic current than larger neurons from group Ia afferent endings (Burke et al. 1976; Fleshman et al. 1981; Heckman and Binder, 1990; Binder et al. 1996).

Alternatively, certain noxious cutaneous inputs may be preferentially distributed to larger motor neurons, which may result in a reversal of the recruitment order (Garnett and Stephens 1980; Garnett and Stephens 1981). Consequently, there has been considerable interest in examining the organization of the synaptic inputs onto the motor neurons.

The classical neurophysiological technique used to determine the organization of the inputs to a neuron involves stimulation of a single presynaptic neuron while recording intracellularly in an expected target neuron. The presence or absence of short latency inhibitory post-synaptic potentials (IPSP) or excitatory post-synaptic potentials (EPSP) can establish if the stimulated neuron projects directly to the target neuron and the strength of connection. Mendell and Henneman (1971) used the spike-triggered averaging technique to determine the magnitude of EPSPs and the extent to which terminals of Ia fibers projected onto the homonymous motor neurons. For this experiment, single Ia fibers originating in the medial gastrocnemius (MG) were activated by electrical stimulation or by stretch of the MG. An intracellular electrode within a MG motor neuron measured responses resulting from the activation of a Ia fiber. Of the single Ia fibers they stimulated, 64% were shown to project to 100% of the sampled homonymous motor neurons. The other 36% of the Ia fibers projected to all but 1 of the motor neurons that were studied. Therefore, it appears wide branching of afferent (Mendell and Henneman 1971) and descending inputs (Somjen et al. 1965; Binder et al. 1996) provides a fairly uniform input to a pool of motor neurons. Consequently, recruitment is primarily dictated by the size principle and proceeds from the smallest to the largest motor units.

Rate Coding

The other means available to the nervous system to increase muscle force besides recruitment is to modulate the firing rate of recruited units. The initial firing rate of a motor unit once it is recruited is between 6 – 12 Hz (Adrian and Bronk 1929; Monster and Chan 1977). From this initial firing rate, the force exerted by a unit can increase from 4 to 10 fold as the firing rate increases until the maximal firing rate is attained (Merton 1954; Milner-Brown et al. 1973b). With increases in synaptic excitation to a pool of motor neurons, active motor units will gradually increase their firing rate and thereby increase force output while new motor units are also recruited (Adrian and Bronk 1929). Consequently, low-threshold motor units typically fire at higher rates than later recruited motor units throughout a contraction of increasing force (De Luca et al. 1982a). Furthermore, it appears that low-threshold motor units attain higher maximal firing rates than later recruited units during a voluntary contraction (De Luca et al. 1982a; Freund et al. 1975; Monster and Chan 1977; Tanji and Kato 1973). The actual maximal firing rate of single motor units, however, has been difficult to measure because of technical limitations in discriminating the discharge of motor units at high forces. Furthermore, maximal firing rate may depend on the species, muscle, and task (Enoka 1995). From the limited data that is available on maximal firing rates during voluntary contractions in humans, it appears that the maximal firing rates can vary between 15 – 50 Hz (Bigland and Lippold 1954; Person and Kudina 1972; Milner-Brown et al. 1973b; Freund et al. 1975; Bellemare et al. 1983).

It has been suggested that the relative contributions of rate coding and recruitment to overall muscle force may vary depending on the function of the muscle. For example, in large muscles such as the biceps brachii that are generally involved in producing large amounts of force, the recruitment of motor units appears to be complete only when the force reaches 80 – 90 % of the maximal force of the muscle (Kukulka and Clamann 1981; Person and Kudina 1972). Alternatively, in hand musculature that is often involved in performing dexterous tasks that require fine gradation of force, recruitment of the motor neuron pool is thought to be complete by 50% of the maximal force output of the muscle (De Luca et al. 1982b). Therefore, increases in force beyond 50% of maximal force is due exclusively to increases in discharge rate. It has been postulated that a narrow recruitment range might be beneficial for the hand muscles in the performance of skilled tasks (De Luca et al. 1985). However, for small forces associated with fine control, a narrowing of the recruitment range may be detrimental to the smooth gradation of muscle force. This is because the force contribution of a motor unit upon recruitment is abruptly altered from zero to approximately 10-25% of the maximal force output for that unit (Merton 1954; Milner-Brown et al. 1973b). Subsequent to this initial step change in force due to recruitment, motor unit force can be altered gradually by rate coding. Therefore, rate coding is associated with a smoother gradation of force and recruitment with a small sudden increase in force. To minimize the disruptions of smooth force gradation as a consequence of recruitment in the low force range recruitment should be distributed over a large force range. Therefore, while the upper limit of recruitment in

hand muscles may be <50% of the maximal muscle force, it is unclear if this has any beneficial effect in the ability to perform tasks of fine control (Fuglevand et al. 1993).

III Cross-Correlation

The distribution of synaptic inputs onto the motor neurons is an important factor in determining their orderly recruitment and is critical in producing coordinated movements of multiple muscles. Intracellular recording and anatomical methods have proved invaluable in revealing input distribution in the animal model but are inapplicable in the human. An indirect method to assess the organization of the inputs to motor neurons in awake animals including humans involves an examination of the temporal relationship between the discharge of two motor units (Sears and Stagg 1976). Theoretically, if two motor neurons are both close to threshold and simultaneously receive an excitatory potential from another neuron which projects to both of them, there is an increased probability that the two neurons will discharge synchronously (Kirkwood and Sears, 1978). Therefore, common projections to neurons result in their synchronous discharge more often than is expected due to chance (Sears and Stagg 1976).

Cross-correlation analysis is the method used to evaluate the degree of synchrony and thereby the extent of common input. Typically, the discharge times of one neuron, termed the event neuron, are plotted relative to the discharge times of a second neuron. The resultant histogram shows the relative firing times of the two neurons and is referred to as a cross-correlogram. A peak in the cross-correlogram around time zero represents the coincidental firing of both neurons greater than expected due to chance (Nordstrom et al. 1992). The magnitude of the synchronous peak is thought to reflect the extent of shared last order inputs to the two neurons (Sears and Stagg 1976).

This approach has been used to understand the organization of last-order inputs to motor neurons controlling hand muscles. The relation in discharge times for two motor units residing in the same muscle has been examined in first dorsal interosseous (FDI) (Bremner et al. 1991a; Datta and Stephens 1990; Milner-Brown et al. 1975; Nordstrom et al. 1992; Semmler and Nordstrom 1995), ED (Schmied et al. 1993), extensor carpi radialis (Schmied et al. 1994) and flexor policus longus (FPL) (Hockensmith and Fuglevand 2000). In the majority of cases, motor units within hand muscles exhibit significant synchrony. This suggests that presynaptic fibers branch extensively across most of the neurons comprising a single motor nucleus (Sears and Stagg 1976).

It is also possible that last-order inputs might be distributed across several motor nuclei. Indeed, the discharge times of motor units in different hand muscles are correlated but the magnitude of the synchrony is usually less than for motor units residing in the same muscle (Bremner et al. 1991b; Gibbs et al. 1995). The importance of these observations is that it reveals that the last-order inputs onto the motor neurons are distributed to more than one motor nucleus involved in a hand movement.

What role might be played by these inputs that supply multiple motor nuclei? One possibility is that the wide spread projections might be a remnant of a dispersed spinal cord connectivity during normal development that play little role in the control of finger movements. Alternatively, this organization might underlie the coordination of multiple muscles needed to perform specific movements. A related question is whether the strength of particular connections of the last-order inputs can be altered by training or habitual use.

To determine the importance of last-order synaptic inputs in coordinating multiple muscles in different movements or motor units within a single muscle, the extent of synchrony for motor unit pairs in different muscles and within the same muscle has been compared during various tasks (Bremner et al. 1991b). Motor unit discharge was recorded for one motor unit of each pair in the FDI while the other unit of each pair was recorded from the second dorsal interosseous. The extent of synchrony for motor unit pairs in these muscles differed during extension versus abduction of the index and middle fingers. This effect of task dependency has also been demonstrated for motor unit pairs within a single muscle. Adams and colleagues (1989) reported a similar finding of task dependency for motor unit pairs in the sternocleidomastoid muscle of the respiratory system.

Given that the organization of last-order presynaptic inputs onto the motor neurons is an integral part of coordinating movements, several investigators have been interested in how these inputs can be shaped with training and experience. For example, it has been speculated that the degree of synchrony for motor unit pairs within a given muscle may be greater in the dominant compared to the non-dominant hand due to greater use. Different investigators have examined this particular issue with varying results. Schmeid and colleagues (1994) found that the degree of synchrony was indeed greater for motor unit pairs in extensor carpi radialis of the dominant arm compared to the non-dominant arm. However, Semmler and Nordstom (1995) have reported that the degree of synchrony for motor unit pairs in FDI was greater in the non-dominant hand of subjects. It is possible that these conflicting results might be explained by differences in the

muscles that were tested. Regardless, it is unclear if an increased use due to handedness is expressed at the spinal level by significant differences in the organization of the last-order synaptic projections onto the motor neurons.

The idea that motor unit synchrony may be strengthened by habitual use and how the central nervous system selects specific combinations of muscles to perform movements was also examined by Hockensmith and Fuglevand (2000). They hypothesized that a high degree of synchrony would exist between motor units in different muscles that flex the index finger and thumb that are commonly used together in the pinch grip. Interestingly, they showed that the degree of synchrony for motor units in different muscles involved in the pinch grip was similar to the extent of synchrony for motor unit pairs residing in FPL. This suggests that the degree of common last-order synaptic inputs across motor neuron pools supplying two muscles was similar to that for motor neurons supplying an individual muscle. Furthermore, the magnitude of the synchrony was greater in the dominant compared to the non-dominant hand. Therefore, the divergence of synaptic input across pools of motor neurons may be an important mechanism by which the central nervous system coordinates the activity of muscles that are commonly used together.

Summary

Experimental findings on the degree of synchrony between motor unit pairs both within and between muscles provide important insights into the organization of the last-order inputs onto the motor neurons. Last-order inputs appear to branch extensively to

several motor nuclei innervating multiple muscles and may play an important role in coordinating those muscles for a variety of movements.

IV Task Groups and Compartmentalization

While the last-order projections onto motor neurons may innervate multiple nuclei, there is compelling evidence that the inputs onto a single motor nucleus may not be uniformly distributed. It has been shown that the recruitment order of motor units within a single muscle may be task specific (Desmedt and Godaux 1981; ter Har Romney et al. 1984). For example, motor units located medially in the long head of the biceps brachii are selectively active during supination of the forearm. In contrast, motor units located in the lateral aspect of the muscle are selectively active during elbow flexion (ter Har Romney et al. 1984). These findings are not consistent with a uniform distribution of synaptic inputs onto the motor nucleus innervating the long head of the biceps brachii. Rather, selective recruitment based on task suggests that the inputs onto the motor neurons are segregated and project to subpopulations of neurons controlling specific movements. Interestingly, the long head of the biceps brachii has no discernable anatomical boundary between muscle fibers activated for elbow flexion and those active for supination of the forearm.

This type of neuromuscular organization is referred to as a task group defined as a collection of efferent and afferent elements that function as a cohesive unit to perform particular tasks (Windhorst et al. 1989). A task group is not defined by specific anatomical boundaries, but rather is defined functionally (Loeb 1985). Alternatively, partitioning of a muscle anatomically, with each compartment often innervated by a separate primary nerve branch is referred to as compartmentalization (English and Weeks 1984). Anatomical compartmentalization has been shown for a variety of muscles in

both the cat and human (English and Weeks 1984; Desmedt and Godaux 1981). For example, the cat lateral gastrocnemius (LG) muscle is anatomically divided into four compartments each supplied by a separate primary nerve branch (English and Weeks 1984). These four anatomical compartments are functionally distinct and exhibit unique patterns of activation during unrestrained locomotion of the cat (English 1984). Furthermore, the motor neurons innervating the different compartments in cat LG are topographically organized within the spinal cord (Weeks and English 1987). Compartmentalization has also been demonstrated by the innervation patterns and muscle fiber architecture in the flexor carpi radialis, extensor carpi radialis longus, LG, and FDI of humans (Segal et al. 1991; Platzer 1992). For example, FDI is an intrinsic hand muscle that is comprised of two distinct heads, which arise from the first and second metacarpal bones (Platzer 1992). The compartmentalization of FDI may contribute to changes in the recruitment order of motor units in FDI during flexion compared to abduction of the index finger (Desmedt and Godaux 1981). These studies provide strong evidence of an anatomical and functional compartmentalization in selected muscles of the cat and human.

Compartmentalization of extrinsic hand muscles

It has been proposed that multi-tendoned extrinsic hand muscles may be compartmentalized and act functionally as several distinct muscles (Fritz et al. 1992). If this organizational scheme were applicable to human ED, it would suggest that ED is divided into four functionally distinct compartments each acting on a specific finger based on the site of attachment of the distal tendons (Windhorst et al. 1989). There is

some anatomical support for the compartmentalization of ED, as the radial nerve branches approximately four times upon entering the muscle (Abrams et al. 1997).

Motor Unit Force Distribution in ED

A corollary to the idea of the compartmentalization of ED is that the force produced by motor units comprising a ED compartment is selective for a single finger. However, data from multitendoned muscles of the cat (Emonet- Dénand et al. 1971; Fritz et al. 1992) and monkey (Schieber et al. 1997) have not supported this idea. In these experiments, force evoked by stimulation of single muscle units or primary nerve branches (Schieber et al. 2001) was distributed across more than one tendon. Perhaps more surprising was the greater degree of selectivity of motor unit force in the multitendoned muscles controlling the cat forepaw than in the homologous muscles controlling the fingers of the monkey (Schieber et al. 1997). It is unclear if human multitendoned extrinsic finger muscles function as a homogeneous unit or as four distinct compartments.

V Organization of inputs to ED

The existence of functional compartments in ED should require that a discreet population of motor units comprise each compartment. Furthermore, such an organizational scheme mandates that each population receives a distinct set of inputs. Such inputs could arise from a variety of sources including descending pathways, interneuronal connections, or afferent feedback. While afferent inputs may project to discreet populations of neurons, these inputs are unable to initiate volitional movements but may help control ongoing movements. Furthermore, it is unlikely that the reticulospinal or lateral vestibulospinal tracts are involved in the control of hand movements as they project primarily to motor neurons controlling proximal musculature (Nyberg-Hansen and Mascitti 1964; Peterson et al. 1979). There is no evidence that the rubrospinal tract has a functional role in man (Nathan and Smith 1982). Consequently, an understanding of the organization of the neural inputs to the motor neurons innervating ED requires a detailed study of the corticospinal pathway which is known to project to motor neurons and interneurons involved in hand control (Porter and Lemon 1993).

The Corticospinal tract

The corticospinal tract of humans is comprised of approximately 1.1 million fibers that originate from pyramidal cells in layer V of the cerebral cortex and projects to the spinal cord (Heffner and Maserton 1975). Historically, the fibers of the corticospinal tract were thought to originate solely in the primary motor cortex (Holmes and May 1909). However, more recently it has been shown in the pig-tailed macaque that only

about 50% of the fibers of the corticospinal tract originate in the primary motor cortex with the other fibers originating in premotor and somatosensory areas (Dum and Strick 1991). In humans, fibers of the corticospinal tract descend through the internal capsule, cerebral peduncle, and medullary pyramids. At the pyramidal decussation, approximately 85% of the fibers cross the midline of the body and descend in the dorsal lateral columns of the contralateral spinal cord (Nolte 1993). It is estimated that 92 % of the fibers comprising the corticospinal tract are small unmyelinated fibers less than 4 μm in diameter (Porter and Lemon 1993). Consequently these fibers have relatively slow conduction velocities of approximately 14 m/s (Kuypers 1981). Conversely, only 2 to 3 percent of the corticospinal tract fibers are larger than 6 μm with the largest fibers having a diameter up to 20 μm. These large myelinated fibers most likely originate from the giant Betz cells of layer V of the primary motor cortex and have average conduction velocities of 60 m/s with the largest fibers being able to conduct up to 80 m/s (Levy et al. 1984).

The primary motor cortex contributes more fibers to the corticospinal tract than any other region. Because of this and the direct projections onto spinal motor neurons, the corticospinal tract has been proposed to play a major role in motor control (Phillips and Porter 1977) and has been heavily studied in primates. Investigators have used a variety of techniques including histological, electrophysiology, lesion, and developmental studies to elucidate the contribution of the corticospinal tract to movement in primates. The results of studies using these techniques with an emphasis on hand movements are summarized in the following section.

Anatomical studies

The termination of the corticospinal tract within the spinal cord has been studied in detail by Kuypers (1981) who postulated that the function of the tract was dictated more by its terminal projections than origin. On the basis of the distribution of the projections of the tract within the spinal cord, Kuypers categorized the mammalian species into four groups. Group 1 includes the ungulates and marsupials in which the corticospinal tract projects to only the cervical or mid-thoracic level and terminates in the dorsal horn. Group 2 is comprised of the cat, rat, dog and some New World monkeys and has terminations of the tract throughout the length of the spinal cord predominantly in the dorsal horn and intermediate zone. Interestingly, direct corticomotoneuronal connections have been shown in the rat (Elger et al. 1977) and therefore may also exist in other species of group 2. Most of the New and Old World monkeys, racoon, and galago comprise group 3 which have corticospinal tract fibers terminating throughout the spinal cord in the dorsal horn, intermediate zone and lateral regions of the ventral horn, wherein reside motor neurons innervating distal musculature. The extent of direct corticomotoneuronal connections within different species that comprise this group is quite variable. For example, in the galago direct corticomotoneuronal connections are scarce, yet in the macaque they are well established. In group 4, which is comprised of the highest group of mammals including man and the great apes, the tract extends throughout the spinal cord and terminates in the dorsal horn, intermediate zone, and ventral horn. Our focus will be predominantly on crossed direct and multi-synaptic connections to motor neurons innervating distal musculature.

Interestingly, it has been found that the overall number of corticospinal tract fibers is not well correlated with dexterity. Rather, it is the number of corticospinal fibers that make direct synaptic contact with motor neurons, namely corticomotoneuronal fibers, that appear to be an important factor associated with performing skilled movements (Heffner and Masterton 1975). Comparisons of the cebus and squirrel monkeys demonstrate an example of the importance of corticomotorneuronal fibers. The cebus monkey has substantial corticomotorneuronal projections (Bortoff and Strick 1993) and displays an ability to manipulate tools and pick up small objects using a "precision grip" (Costello and Fragaszy 1988). In comparison, squirrel monkeys have sparse corticomotorneuronal projections (Bortoff and Strick 1993) and grasp small objects using a "power grip" in which all of the fingers close around the object in unison (Costello and Fragaszy 1988). Further indirect evidence of the importance of corticomotoneuronal connections is the observation that corticospinal projections to the ventral horn are most prominent in the grat apes and man (Kuypers 1981). While this evidence is purely correlative, it does suggest that corticomotoneuronal connections are to some extent responsible for the ability to perform dexterous tasks.

Lesion studies

The corticospinal tract and corticomotorneuronal connections are believed to be critically important in the generation of dexterous hand movements. Consequently, many investigators have studied the behavior of primates before and after lesions of the corticospinal tract. For example Lawrence and Kuypers (1968 a, b) investigated the effects of lesions of the corticospinal tract either bilaterally or unilaterally at the level of

the pyramids in rhesus monkeys. In animals that received a bilaterally pyramidotomy, the arms and hands were initially very weak. With time, the monkeys re-gained strength in their upper limbs and were able to firmly grip the cage bars. The dexterity of finger movements was judged by the ability of the animals to retrieve food from wells of different diameter. While the dexterity of the monkeys gradually improved allowing them to extract food from the larger wells, they did not regain the ability to retrieve food from smaller holes. The inability to grasp food from the smaller holes appeared to be the result of an inability to move their fingers independently. Therefore, the corticospinal tract appears to play an important role in the coordination and independence of finger movements, as these functions are highly impaired when the tract is lesioned.

Electrophysiological evidence

While anatomical techniques demonstrated that some of the terminal projections of the corticospinal tract are in the ventral horn, this was not sufficient proof of direct corticomotoneuronal connections. Proof of corticomotoneuronal connections was first obtained by Bernhard et al. (1953), who applied electrical stimulation to the cortex of the monkey while recording the evoked response in dorsal lateral columns of the contralateral spinal cord and contralateral ventral roots of several peripheral nerves. Based on the difference in latency of response at both sites from the delivery of the stimulus, they deduced that the corticospinal fibers synapse directly onto the spinal motor neurons. The authors coined the term of 'corticomotorneuronal' fibers to describe the origin and unique termination of these fibers. They further speculated that this

monosynaptic pathway might play an important role in dexterous movements with the hands.

The results of Bernhard were confirmed by intracellular recordings of post-synaptic potentials in spinal motor neurons in response to weak electrical stimulation of the cortex in monkeys (Preston and Whitlock 1961). Electrical stimulation was successful in eliciting excitatory post-synaptic potentials (EPSPs) in spinal motor neurons innervating hand muscles with a latency consistent with a monosynapic connection from the motor cortex. Subsequently, it was established that inhibitory post-synaptic potentials (IPSPs) involved disynaptic pathways via inhibitory spinal interneurons (Jankowska et al. 1975).

Techniques other than intracellular recordings have been used to verify the existence of monosynaptic connections from the cortex to spinal motor neurons. One technique involves extracellular recording of the discharge of a pyramidal cell in layer V of the motor cortex and to use the discharge times to spike-trigger average the surface EMG of active muscles. The cortical neuron will produce an EPSP in the population of motor neurons with which it has a monosynaptic connection. Consequently, the EPSP produced by the cortical neuron will raise the probability of firing in the associated motor neurons. This increased firing probability should manifest itself as an increase in the surface EMG at the appropriate latency detectable with spike-triggered averaging and is known as post-spike facilitation. The latency of the post-spike facilitation suggests that the effects are mediated by large diameter fibers of the corticospinal pathway with direct projections onto the motor neurons (Fetz and Cheney 1980; Lemon et al. 1986; Lemon 1993). Furthermore, it has been shown that a single cortical neuron can produce post-spike

faciliation in many different muscles that control the hand and wrist. This finding suggests that a single pyramidal cell may have monosynaptic connections onto several different motor neuron pools. This finding is consistent with anatomical observations (Shinoda et al. 1981) and cross-correlation studies (Bremner et al. 1991a). Indirect support that the post-spike facilitation is mediated by monosynaptic connections is derived from comparative studies of cats, which lack direct corticomotorneuronal connections and report longer post-spike facilitation latencies (Armstrong and Drew 1984).

Finally, both transcranial electrical and magnetic stimulation have been used to show the existence of rapidly conducting corticospinal fibers with direct projections to the motor neurons innervating hand muscles (Merton and Morton 1980; Marsden et al. 1983; Rothwell et al. 1987). Stimulation of the human motor cortex by either of these methods produces a short latency muscle evoked potential in the contralateral limb muscles. The latency of the evoked potentials is consistent with activation of the largest diameter fibers of the corticospinal tract with monosynaptic connections onto spinal motor neurons.

Developmental studies

The importance of the corticospinal tract in the production of highly skilled hand movements has also been assessed by correlating the behavior of infants with the development of corticospinal connections. In human infants the ability to produce independent finger movements coincides with the age that a normal latency and activation threshold for transcranial magnetic stimulation over the motor cortex is established at around 18 to 24 months (Eyre et al 1991). In both humans and monkeys,

the short-latency excitation of the upper limb muscles due to transcranial magnetic stimulation occurs via the corticospinal pathway (Edgley et al. 1990; Palmer and Ashby 1992). Presumably, the development of the corticospinal tract continues during post-natal development allowing for the evolution of skilled movements of the hand and fingers.

Lesions of the corticospinal tract in infant monkeys have been performed which prevented the normal connections from developing. It was observed in these animals that their general motor skills developed normally with the exception of a significantly diminished ability to perform skilled movements with their hands. For example, these monkeys were never able to move their fingers independently (Lawrence and Hopkins 1976). Given these observations associated with normal development and behavioral deficits arising when the corticospinal tract is prevented from developing, it appears that the direct projections of the corticospinal tract onto the motor neurons are extremely important in the performance of skilled finger movements.

Conclusions

From an evolutionary standpoint, the development of the corticospinal tract in mammals is one of the key features of the primate motor system. In primates, the role of the cortical spinal tract has increased while the contribution of other descending pathways such as the rubrospinal tract has decreased. One critical advance in the evolution of the corticospinal tract has been the development of direct monosynaptic linkages between the motor cortex and the spinal motor neurons. The correlation between the increased corticomotorneuronal connections in the higher primates and dexterity of the hand is

indirect evidence of the importance of these connections in performing fine motor tasks with the hand. Furthermore, the time course in the development of the corticomotorneuronal connections in infants parallels the increasing behavioral abilities of infants to perform fractionated finger movements.

VI The Primary Motor Cortex

The previous section dealt primarily with motor functions associated with the corticospinal tract but provided little information on the origin of the tract. In primates, the corticospinal tract originates from several motor areas, which include somato-sensory cortex within the parietal lobe, premotor areas, and the primary motor cortex. Corticospinal projections from the parietal lobe are sparse and terminate almost exclusively in the dorsal horn (Coulter and Jones 1977) and therefore may be important for processing sensory information. The premotor cortex is comprised of multiple, distinct premotor areas located in the arcuate sulcus, superior precentral sulcus, cingulate sulcus and superior frontal gyrus, which project to both the primary motor cortex and spinal cord (Dum and Strick 1991). Many functions have been associated with the premotor areas, including bimanual coordination (Brinkman 1984), preparation for movement (Passingham 1988), and movement sequencing (Roland et al. 1980). Clearly, both the sensory and premotor areas are important in the function of the motor system and together with the primary motor cortex comprise the motor cortex. However, it is the primary motor cortex that contributes more fibers to the corticospinal tract than any other region (Porter and Lemon 1993). Consequently, it is speculated that the primary motor cortex may be particularly important in the control of hand movements.

The primary motor cortex is located rostral to the central sulcus and is the thickest region of the cerebral cortex in man and macaque monkey with the lowest neuronal density (Phillips 1981; Rockel et al. 1980; Sholl 1956). The cerebral cortex is a covering of neurons and their interconnections a few millimeters thick over the cerebral

hemispheres and is comprised of the neocortex, paleocortex, and archicortex. The neocortex represents most of the cortex on the outside of the brain accounting for more than 90% of the total cortical area and is organized as a six-layered structure (Nolte 1993). While pyramidal cells are found throughout layer V of the neocortex, the primary motor cortex contains the largest ones. In humans these distinctive cells can have soma diameters up to 120 μm (Meyer 1987) and are estimated to receive up to 60, 000 inputs (Cragg 1975). The pyramidal cells of the motor cortex project to the spinal cord brainstem, and other cortical areas. However, only 10 – 20% of the pyramidal cells located in layer V of the primary motor cortex send axons which comprise the corticospinal tract (Landgren et al. 1962).

Stimulation of the Motor Cortex

Fundamental to our understanding of motor control is knowledge of how the motor cortex engages spinal circuits to produce volitional movements. To gain insight into this matter, investigators have activated neurons in the motor cortex artificially using electrical stimulation and recorded the evoked movement. In the 1920's – 1930's, Penfield performed a comprehensive intracortical stimulation study of the motor cortex in 163 conscious human patients suffering from epilepsy (Penfield and Boldrey 1937). He reported that motor responses were consistently evoked in the contralateral side of the body in response to stimulation rostral to the central sulcus. By correlating electrode locations with evoked motor responses, it was evident that a rough topographical map of the body existed in the motor cortex with large areas devoted to movements of the hand and face. Penfield did make note of extensive variability between patients in the

topographical position of body segments (Penfield and Boldrey 1937). The result of much of Penfield's work was summarized in a famous figure depicting a highly organized homunculus of the motor cortex (Penfield and Rasmussen 1952). For example, this figure depicts the hand area of the motor cortex being divided into discreet regions dedicated to individual digits. One interpretation of this schematic representation is that movements of individual fingers might be accomplished by activation of a specific region of the primary motor cortex. Each finger region then would project to the pool of motor neurons innervating the appropriate muscles capable of producing the desired finger movement. This "labeled-line" hypothesis provided clinicians and scientists with a simple explanation for the control of movements of the hand and other body segments (Schieber 1996).

However, intracortical microstimulation of the hand area of the primary motor cortex evokes movements of several digits with selective movements of an individual digit being rare (Woolsey et al. 1979). Furthermore, identical movements can be elicited by microstimulation within the primate motor cortex in multiple noncontiguous zones (Woolsey et al. 1979; Donoghue et al. 1992; Nudo et al. 1996). These findings are not consistent with a strict topographical representation of individual digits within the primary motor cortex. Consequently, the contemporary view of the hand area of the motor cortex is as an integrated network distributed in a mosaic fashion that projects to interneurons and motor neurons involved in hand control (Schieber and Hibbard 1993; Schieber 1996).

Lesion Studies

In addition to stimulation, investigators have also gained insight into the role of the motor cortex by producing lesions of the primary motor cortex and noting deficits in movement. Lesion studies have been performed on a variety of species with diverse results. For simplicity, the focus of this section will be limited to lesions of the motor cortex hand area within the primate.

In a classic study by Leyton and Sherrington (1917), extensive hemispheric removal of the motor cortex dedicated to hand movements was performed in young chimpanzees. The anatomical result was degeneration of pyramidal tract fibers. The animal exhibited a flaccid paralysis of the contralateral hand and often would use only the non-affected limb. Remarkably, over several weeks the animal gradually improved motor function in the affected limb until many of the original deficits were undetectable. A similar result was reported in squirrel monkeys that underwent focal ischemic infarcts of the primary motor cortex and demonstrated no motor deficits two months post-operatively (Nudo and Milliken 1996).

Other investigators who have induced lesions to primary motor cortex have also reported an initial impairment in the contralateral hand followed over time by a partial but not complete return of motor function in the affected limb. Persistent deficits in monkeys include a slowness of movements (Travis 1955), weakness in the contralateral hand (Glees and Cole 1950), and a decrement in dexterity when attempting skilled tasks with the fingers (Glees and Cole 1950; Travis 1955; Bioulac et al. 1995; Rouiller et al. 1998). Clinical observations of humans who have suffered lesions of the motor cortex as

a result of a stroke often include long-lasting deficits in the ability to move fingers independently of the contralateral hand (Twitchell 1951).

Several mechanisms may be responsible for the recovery of motor function following injury of the primary motor cortex. For example, Glees and Cole (1950) found that motor cortex surrounding the lesion of the hand area underwent a functional reorganization and elicited hand responses evoked by microstimulation which were not detectable prior to the lesion. However, reorganization of the intact cortex adjacent to a cortical lesion is not always found (Nudo and Milliken 1996) but appears to require rehabilitative training (Nudo et al. 1996). One potential mechanism that might explain some of the remarkable compensation to injury to the motor cortex is the existence of undamaged pathways to the spinal cord including uncrossed fibers from the ipsilateral motor cortex, corticospinal tract fibers originating in premotor areas or sensory areas, and fibers from subcortical centers (Travis 1955; Nudo and Milliken 1996; Rouiller et al. 1998). Despite extensive study over the past century, the specific neurophysiological mechanisms of a partial or complete recovery of function after ablation of the primary motor cortex is still unclear.

Temporary inactivation has also been used to examine the topograpical organization of the primary motor cortex in monkeys (Poliakov and Schieber 1999). Localized intracortical injections of muscimol were given in the hand area of the motor cortex while trained monkeys performed individuated finger movements. Little evidence was found that the impaired finger or fingers were related to the location along the central sulcus

that was inactivated. These results suggest that the control of individuated finger movements is distributed throughout the hand area of the motor cortex.

Single Cell Recordings

One limitation in interpreting results from denervation or intracortical stimulation studies is that these methods affect many cortical neurons. For example, it is estimated that a current of 5 μA, a minimal current used during microstimulation, may excite up 900 small and 5 large pyramidal cells (Andersen et al. 1975). Therefore, to better understand how the motor cortex is organized to command movement, investigators have recorded single cell behavior in a variety of species during a wide range of motor behaviors from locomotion to finger movements.

What does the motor cortex encode?

The initial extracellular recordings of neurons in the motor cortex of monkeys demonstrated a relatively linear relationship between cellular activity and muscle force during wrist flexion and extension movements (Evarts 1968; Evarts 1969). Subsequently, several investigators have confirmed this relationship using a precision grip task (Hepp-Reymond et al. 1978; Hepp-Reymond and Diener 1983; Wannier et al. 1991; Maier and Hepp-Reymond 1995). These studies concluded that the motor cortex encodes an intrinsic parameter such as muscle force or joint torque.

Alternatively, the motor cortex may encode movement in a reference frame that is external or extrinsic to the body. Such extrinsic coding of movement has been demonstrated in a series of studies by Georgopolos and colleagues (Georgopoulos et al. 1982; Georgopoulos et al. 1986; Georgopoulos et al. 1988; Georgopoulos et al. 1989;

Georgopoulos et al. 1992). Neurons recorded from monkey primary motor cortex during reaching movements appeared to be broadly tuned to movement direction with each neuron firing maximally for a "preferred" direction. Because of the broad directional tuning, many neurons in the primary motor cortex were active for any direction of movement. Calculation of a population vector from the active neurons during a movement predicted a movement direction in close proximity to the actual movement. However, it has been argued that this directional tuning in extrinsic coordinates is simply a by-product of activating the musculature (an intrinsic parameter) necessary for movement in a particular direction (Scott 2000).

A clever experiment by Kakei et al. (1999) tested these competing ideas of the motor cortex encoding either muscle activity or movement direction. Neurons in the primary motor cortex in monkeys were recorded during movements of wrist flexion or extension with the forearm in either a fully supinated or pronated position. This paradigm dissociated the muscles involved from the extrinsic direction of movement. For example, a downward (extrinsic) movement of the wrist is produced by wrist flexion when the forearm is pronated but by wrist extension when the forearm is supinated. Kakei and colleagues reported that half of the cortical neurons responded to the extrinsic parameter of direction, 32% of the cells encoded the intrinsic parameter of musculature, and they were unable to classify the remaining 18%. They concluded that the motor cortex contains at least two distinct groups of neurons which respond to different parameters of movement. Consequently, the specific parameters of volitional movement that are

represented by neuronal activity in the primary motor cortex probably include both muscle activity and movement direction.

Absence of Motor Cortex Somatotopy Revealed by Intracortical Recordings

Results from single cell recordings within the hand area of the primary motor cortex of the monkey are inconsistent with a highly organized somatotopy. Schieber and Hibbard (1993) found that the majority of neurons were active during two or more instructed movements of the digits. Furthermore, active neurons were found distributed throughout the hand area of the primary motor cortex during each instructed movement of the digits (Schieber and Hibbard 1993). These findings further support the idea that each finger movement may be specified by a neuronal population distributed throughout the hand area of the primary motor cortex.

Summary

Results from microstimulation, lesions and intracortical recordings of the primary motor cortex have shown that a strict topographical mapping of the individual digits does not exist. Furthermore, the specific movement parameter encoded by the primary motor cortex has proven to be elusive. Currently there is no consensus as to whether the primary motor cortex commands an intrinsic parameter such as muscle activity or a more abstract extrinsic parameter such as movement direction. However, it is known that damage to the hand area of the primary motor cortex results in impairments in the fine control of the contralateral hand with recovery apparently dependent on the severity of the lesion, training and neural plasticity.

VII Summary of Research Aims

Many factors such as the activation of neurons in the primary motor cortex, distribution of the synaptic inputs from descending pathways onto spinal interneurons and motor neurons, and neuromuscular compartmentalization must be considered in attempting to understand how finger movements are accomplished. The experiments described in this dissertation aim to advance our knowledge about the control of finger movements by examining the neural and muscular organization of one of the primary muscles involved in moving the fingers, the human extensor digitorum (ED).

As mentioned previously, ED is a single-bellied muscle that gives rise to four parallel tendons and may be comprised of four distinct functional compartments (Fritz et al. 1992). Each compartment may be controlled by a separate set of motor neurons which innervate muscle fibers that produce force on one of the tendons emanating from ED. Such an arrangement would provide the substrate for independent extension of the fingers. A corollary of this idea is that the force contributed by a single motor unit in ED should be highly selective for a particular finger. Therefore, the first aim of this dissertation is to determine how the force from single motor units in ED is distributed across the fingers. This issue is discussed in chapter 3.

This dissertation also examines musculotendonous and neural factors that influence the extent to which ED functions as a compartmentalized muscle. Anatomical studies of the hand reveal lateral connections between the distal tendons emanating from ED. The degree to which the connections between the distal tendons of ED distribute force across the fingers is explored in chapter 4. Synchronous activity of motor units in different

compartments may also underlie a form of neural coupling that may limit the ability of the fingers to move independently. Therefore, chapter 5 of this dissertation addresses whether motor units located in different compartments of ED discharge synchronously more often than expected due to chance. Finally, the anatomical organization of muscle fibers belonging to single motor units comprising ED may also influence how motor unit force is distributed. Therefore, the last aim of this dissertation, presented in chapter 6, is to determine whether and the extent to which motor axons branch to innervate muscle fibers in multiple compartments of ED.

CHAPTER 3

SPIKE-TRIGGERED AVERAGING REVEALS MECHANICAL COUPLING OF EXTENSOR DIGITORUM MOTOR UNITS ACROSS DIGITS OF THE HUMAN HAND

INTRODUCTION

Humans display remarkable dexterity of their fingers that may best be exemplified by a skilled musician such as a pianist or guitar player. This dexterity is derived in large part from the ability to move the fingers relatively independently and is not limited to humans. Nonhuman primates such as monkeys are also capable of manipulating objects with their fingers in highly skilled tasks. Surprisingly, the primary extensors and flexors of the fingers in primates are extrinsic muscles that give rise distally to multiple parallel tendons that insert onto all the fingers. Consequently, activation of these muscles might be expected to produce movement in all of the fingers rather than individuated movements.

Current thinking, however, is that the primary finger flexors and extensors are comprised of distinct functional compartments. Each compartment is thought to be controlled by a separate set of motor neurons which activate muscle fibers that exert force onto one of the tendons emanating from the muscle and thereby provide independent control of the digits (Fritz et al. 1992). Support for this idea comes from magnetic resonance imaging of extrinsic flexor muscles in humans which has shown that these muscles appear to be comprised of different subdivisions that participate in the flexion of specific digits (Fleckenstein et al. 1992).

Accordingly, force produced by a single motor unit in these multi-tendoned muscles should be highly selective for a particular digit. In homologous muscles that control the cat distal forelimb and fingers of the monkey, motor unit force has been shown to be preferential, but not exclusive to a particular tendon (Schieber et al. 1997). Therefore, the

initial goal of this dissertation was to examine the force distribution across the four fingers for motor units in human extensor digitorum (ED), a multi-tendoned muscle that extends the fingers. Knowledge of how motor unit force is distributed across multiple tendons is crucial for understanding the neuromotor control strategies used to perform individuated finger movements.

METHODS

Twenty-two experiments were performed on the right ED muscle in 12 healthy human volunteers (5 female, 7 male, ages 22-39 years). The experimental procedures were approved by the Human Investigation Committee at the University of Arizona. All subjects gave their informed consent to participate in the study. Subjects were seated comfortably in a dental chair with their right elbow and wrist supported and immobilized (Figure 1). The elbow was flexed at an angle of approximately 150 degrees and maintained with the right hand oriented midway between fully supinated and fully pronated with the thumb pointing upwards. With the hand in this orientation, gravity had little effect on the extension force produced by the fingers. The wrist was stabilized by padded vertical posts placed on either side of the distal forearm and the dorsal and palmer aspects of the hand. The posts were secured to the experimental platform by magnets that could be inactivated to allow for their positioning. The metacarpophalangeal joints were maintained at a joint angle of approximately 90 degrees by metal cuffs around the proximal interphalangeal joints that were attached to separate force transducers via light cables. The metal cuffs were individually fitted for each digit. The length of each cable was adjusted at the beginning of the experiment so that each digit was preloaded in this

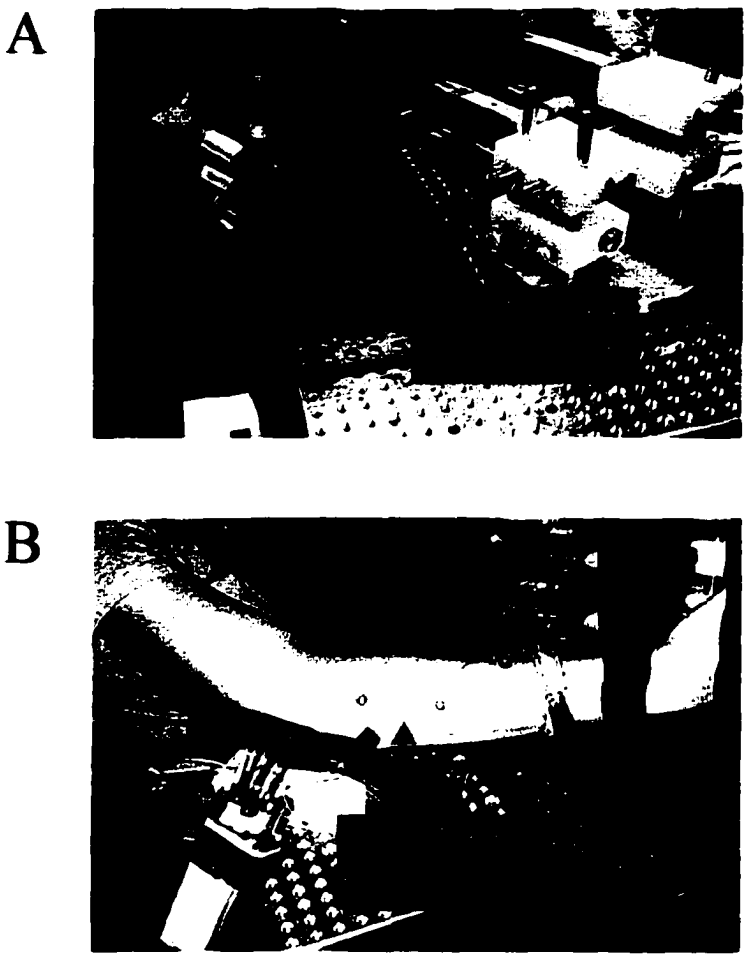

FIGURE 3.1 Front (A), and side (B) views of experimental set-up. Elbow and forearm were supported on an adjustable stand. The hand and wrist were stabilized by padded bars that extended from adjustable magnetic stands. A) Each finger was attached to a separate force transducer by a cable attached to a metal cuff surrounding the finger. The MCP joints of the fingers were maintained in a flexed position with a preload of ~ 2 N to maintain ED in a lengthened position. B) A tungsten microelectrode was inserted into ED. A surface electrode over the radius was used as a reference for the tungsten electrode. Two surface electrodes were located over ED to record global EMG activity, however, the data recorded by these electrodes were not used in the data analysis.

flexed position with a force of approximately 2 N. The fingers were flexed in order to lengthen ED and thus optimize the force output of this muscle. For some subjects, small pieces of foam were inserted between the fingers (not shown in Figure 1) near the MCP joint in order to prevent the fingers from contacting one another.

Force and EMG recording

Extension force of the digits was measured by four force transducers (Grass Instruments, Warwick, Rhode Island, model FT-10, range 0 – 5 N, sensitivity 780 mN/mV) mounted in a custom built manipulandum. This design allowed each transducer to be aligned both horizontally and vertically with the proximal interphalangeal joint of the appropriate finger. The force signals were amplified (X 1000) (World Precision Instruments, Sarasota, Florida) and displayed on an oscilloscope. Motor unit action potentials were recorded with sterilized tungsten microelectrodes inserted into ED (Frederick Haer & Co. Bowdoinham, Maine, 1- to 5-μm tip diameter, 5- to 10-μm uninsulated length, 250-μm shaft diameter, ~ 200 kΩ impedance at 1000 Hz after insertion). A surface electrode (4 mm diameter Ag-AgCl) attached to the skin overlying the radius served as a reference electrode for the intramuscular electrode. The intramuscular electromyographic (EMG) signals were amplified (X 1000), band pass filtered (0.3-3 kHz) (Grass Instruments, Warwick, Rhode Island), and displayed on an oscilloscope.

Protocol

Subjects performed a weak isometric extension of all four fingers in order to activate ED while the microelectrode was manipulated until the action potentials of a motor unit

could be clearly identified. Once a motor unit was identified, the subject sustained a weak contraction of ED to maintain the unit discharging at a minimal rate. The intramuscular EMG and extension force of each finger were recorded for three minutes or until the motor unit could no longer be clearly discriminated. The extension force of each digit during this task was usually less than 1 N. The subject received visual and auditory feedback on the discharge of the motor unit and one to two minutes of rest between recordings. After each recording, the microelectrode position was readjusted which occasionally included removal of the microelectrode and reinsertion at a new site until the action potentials of presumably a new motor unit could be identified. Successive trials were performed for up to two hours. Extension force of each finger and intramuscular EMG were digitally sampled at approximately 2 and 18.5 kHz, respectively, using the Spike2 data acquisition and analysis system (Cambridge Electronics Design, Cambridge, England).

Data Analysis

Data were analyzed off-line using Spike 2 and custom designed software. Motor unit discrimination was accomplished using a template-matching algorithm based on waveform shape and amplitude. An event channel representing the timing of discharges of accepted action potentials for a motor unit was generated. The event channel was used as a trigger to send a brief time segment (140 ms, 15 ms pre-trigger) of each force channel to an averaging algorithm (Stein et al. 1972; Stephens and Usherwood, 1977). The resulting spike-triggered average of each force channel provided an estimate of the force transient contributed by the reference motor unit to each of the fingers. Peak force

and time to peak force (contraction time), measured from the initial rise in force, were determined from the spike-triggered average force profile of each finger. Total motor unit force was calculated as the sum of the peak force across all fingers. Motor unit contraction time was calculated as the mean contraction time for the four fingers. If a motor unit produced no force on a digit, the contraction time for that digit was omitted.

A selectivity index (Schieber et al. 1997) was used to quantify the distribution of motor unit force across the four digits. The selectivity index is calculated from the force produced on each finger as:

$$\text{selectivity index} = d / d_{\max}$$

$$\text{where } d = \sqrt{\sum_{i=1}^{n} (\tau_i - \tau_u)^2}$$

$$\text{and } d_{\max} = \sqrt{(1 - \tau_u)^2 + \sum_{i=2}^{n} (0 - \tau_u)^2}$$

where τ_u is equal to one divided by the number of tendons emanating from the muscle or in our case 0.25, and τ represents the amount of force produced on each of the fingers (i). For example, if a single motor unit produced forces of 4 mN, 4 mN, 2 mN and 0 mN, on the index through little finger, respectively, then $\tau_1 = 4$, $\tau_2 = 4$, $\tau_3 = 2$, and $\tau_4 = 0$. Consequently the selectivity index for this unit would be 0.383. A selectivity index of one represents a motor unit that transmits all of its force to only one finger. At the other extreme, a selectivity index of zero indicates a motor unit that distributes its force evenly across all fingers. A preferred finger was designated for each motor unit based on the digit to which the unit exerted the most force. A one way ANOVA was used to compare

the selectivity index across fingers. Values are reported as means ± standard deviation with a probability of 0.05 selected as the level of statistical significance.

RESULTS

The current chapter reports the contractile properties and force distribution across the four fingers for 233 motor units in human ED based on spike-triggered averaging. An average of 10.6 ± 4.5 motor units were recorded per experimental session. A sample recording of approximately 8 seconds extracted from a three minute record is shown in Figure 2. The lower four traces from the bottom up are the force recordings for digits 2 through 5 (index, middle, ring, and little fingers, respectively). Directly above the force records is the intramuscular EMG trace depicting the discharge of a single unit. The discharge times of the unit were identified and used to plot the instantaneous frequency and is shown above the intramuscular EMG trace. An arterial pulse pressure artifact is evident in the force trace of digit 5. Spike-triggered averaging of the four force channels was utilized to obtain an estimate of the force transients exerted by each motor unit on each finger. The average number of events used for spike-triggered averaging was 1072 ± 592 with a range of 52 to 3194.

Contractile Properties

Examples of the spike-triggered average force developed on each finger are shown in Figure 3 for four different motor units each with different preferred fingers (digits 2 through 5, Figs 3A, 3B, 3C, 3D, respectively). All of these units exhibited a broad force distribution with selectivity index values of 0.33, 0.32, 0.34, and 0.33 and had a total

motor unit force of 6.0 mN, 28.8 mN, 12.3 mN and 11.9 mN (Figs. 3A, 3B, 3C, 3D respectively).

The mean total motor unit force for the 233 units studied was 11.4 ± 9.7 mN with a range from 0.5 to 53.8 mN (Figure 4). The total force for the recorded population of motor units was skewed toward low-forces with a median value of 8.9 mN compared to a mean value of 11.4 mN. These force values are similar to those reported in human ED by Monster and Chan (1977) with a mean estimated from their Figure 8 to be approximately 13.7 mN with forces also skewed toward small values. The mean motor unit force in the present study is also similar to that reported in intrinsic hand muscles obtained by intraneural stimulation of the thenar muscles (11.3 mN, Thomas et al. 1990a) and spike-triggered averaging of first dorsal interosseous (17.4 mN, Galganski et al. 1993).

The mean contraction time for motor units recorded in the present study was 43.2 ± 8.6 ms, which was slightly briefer than that previously reported for the extrinsic finger flexors (Fuglevand et al. 1999) or toe extensors (Macefield et al. 1996) using intraneural stimulation. The shorter contraction times may be partly a consequence of spike-triggered averaging (Andreassen and Bar-On 1983; Calancie and Bawa 1986; Nordstrom et al. 1989) or may represent differences in contractile properties for motor units in different muscles. No significant correlation between contraction time and motor unit force was found (Figure 5), which is consistent with that reported previously for motor units in other human muscles (Fuglevand et al. 1999; Macefield et al. 1996; Thomas et al. 1990b).

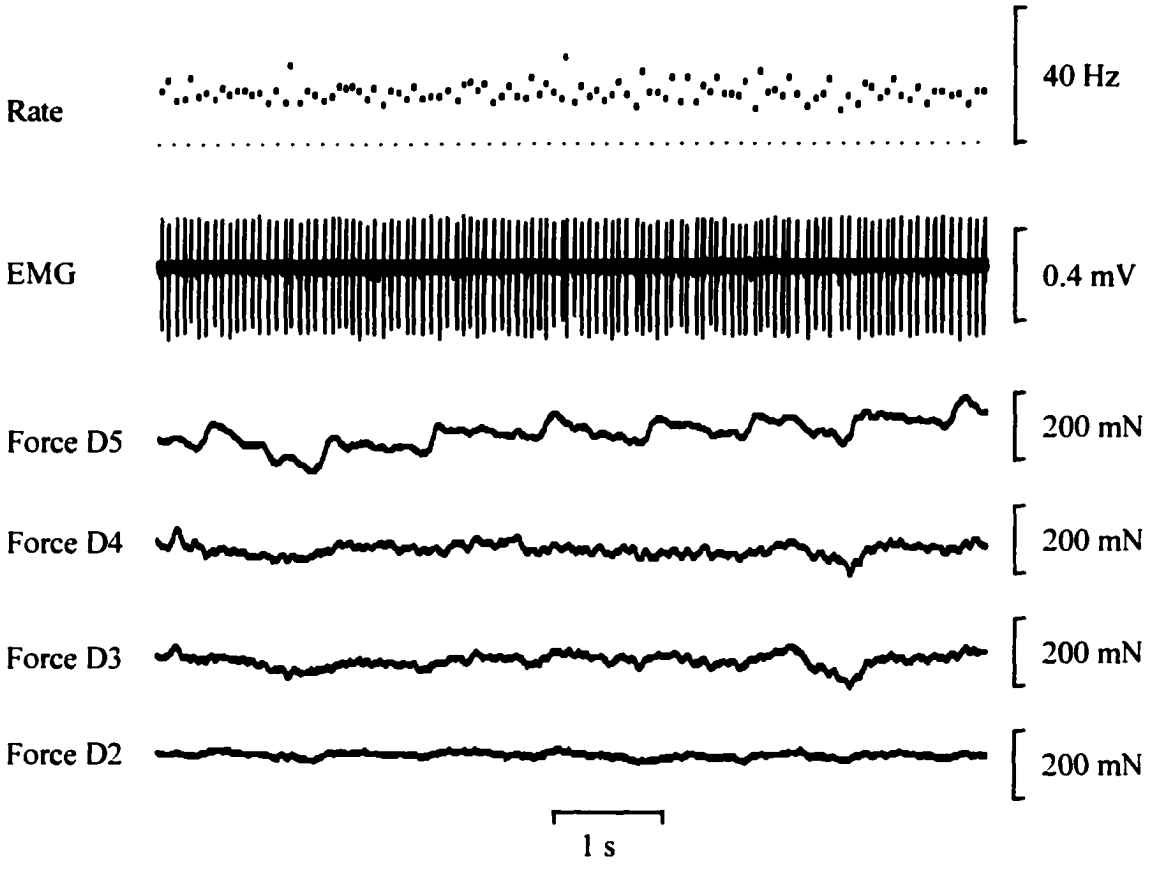

FIGURE 3.2 Sample data showing simultaneous recording of finger extension force from digits 2 through 5 and motor unit activity in ED. The lower four traces from the bottom up are the force recordings for digits 2 through 5, respectively. The large force transient on D5 is an arterial pulse-pressure artifact. Directly above the force records is an intramuscular EMG trace recorded with a tungsten microelectrode depicting the discharge of a single unit. The discharge times were identified and used to plot the instantaneous frequency and is displayed in the top trace.

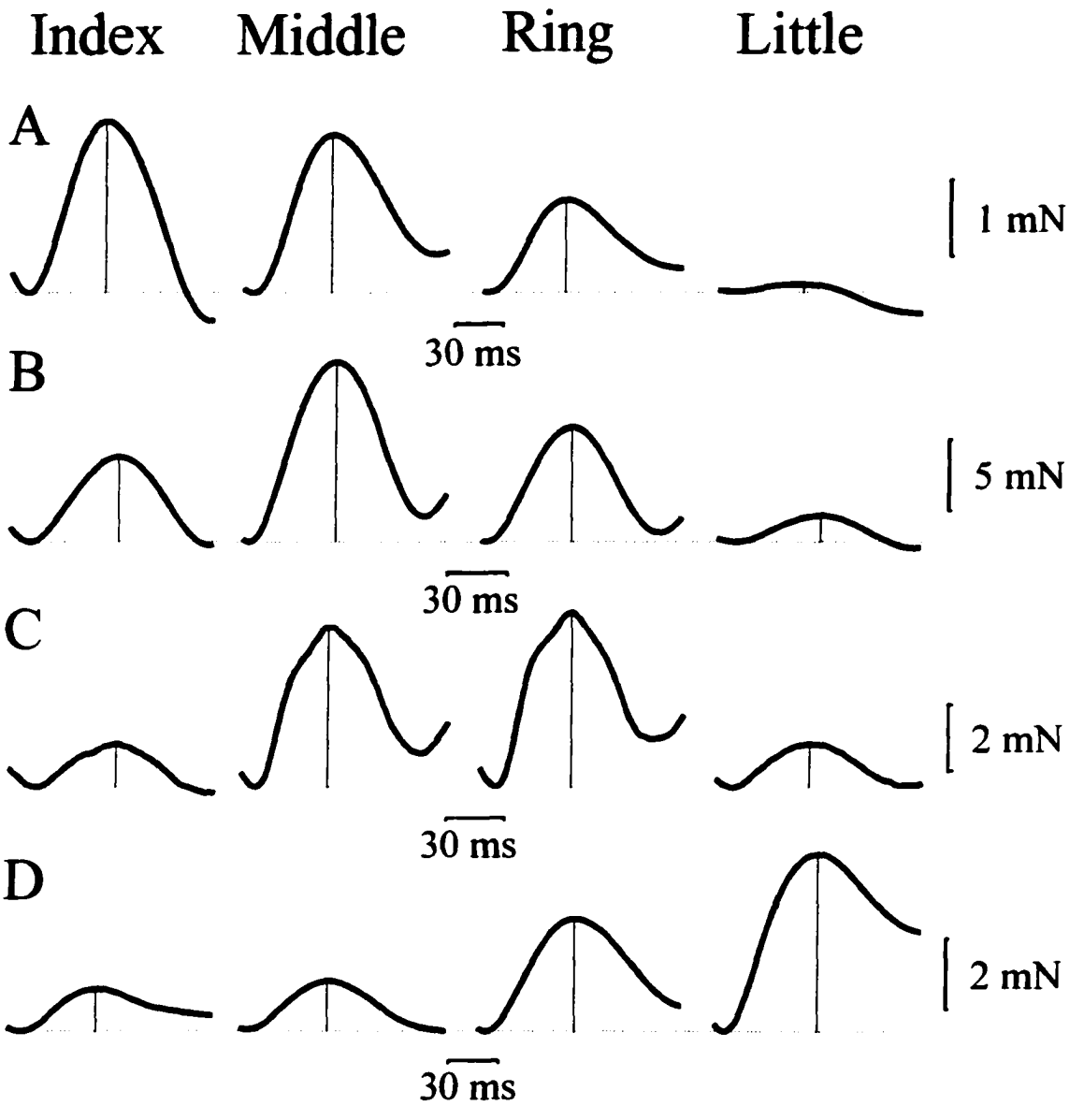

FIGURE 3.3 Examples of the spike-triggered average forces from four ED motor units. Each of these motor units show a characteristic broad distribution of force across the digits. Motor units were categorized based on the digit in which the greatest force was produced. These motor units were categorized to have digits 2 through 5 as preferred fingers (A – D) with selectivity index values 0.33, 0.32, 0.34, and 0.33, respectively.

Force Distribution

The mean selectivity index for all motor units recorded was 0.38 ± 0.14 with a range from 0.09 to 0.79 (Figure 6). These low values for the selectivity index indicate that the force of single motor units in ED is broadly distributed across the digits. Moreover, no motor unit in the present study had a selectivity index greater than 0.8, indicating that no unit transmitted all of its force to only one finger.

Motor units were categorized according to the digit upon which they produced the greatest force, referred to as the preferred finger. Using this classification scheme, 39, 93, 63, and 38 motor units were designated as the preferred fingers of digits 2 through 5, respectively. There was no statistical difference in the selectivity index across motor unit groups based on preferred finger (mean selectivity index of motor units for preferred fingers of digits 2 through 5 was 0.4 ± 0.15, 0.4 ± 0.12, 0.37 ± 0.16, and 0.37 ± 0.13, respectively). Because no difference in the selectivity index was found between digits, the data were combined across fingers. The grouped data showed a significant correlation between motor unit force and selectivity ($P = 0.003$) with stronger motor units tending to have lower selectivity indices (Figure 7). However, this result should be interpreted with caution because of a low correlation coefficient ($r = -0.19$). Overall, selectivity did not vary across fingers but was negatively correlated, in a modest way, to motor unit force.

DISCUSSION

The main finding of this study was that spike-triggered average forces of motor units in human ED were broadly distributed across the fingers. In fact, none of the motor units

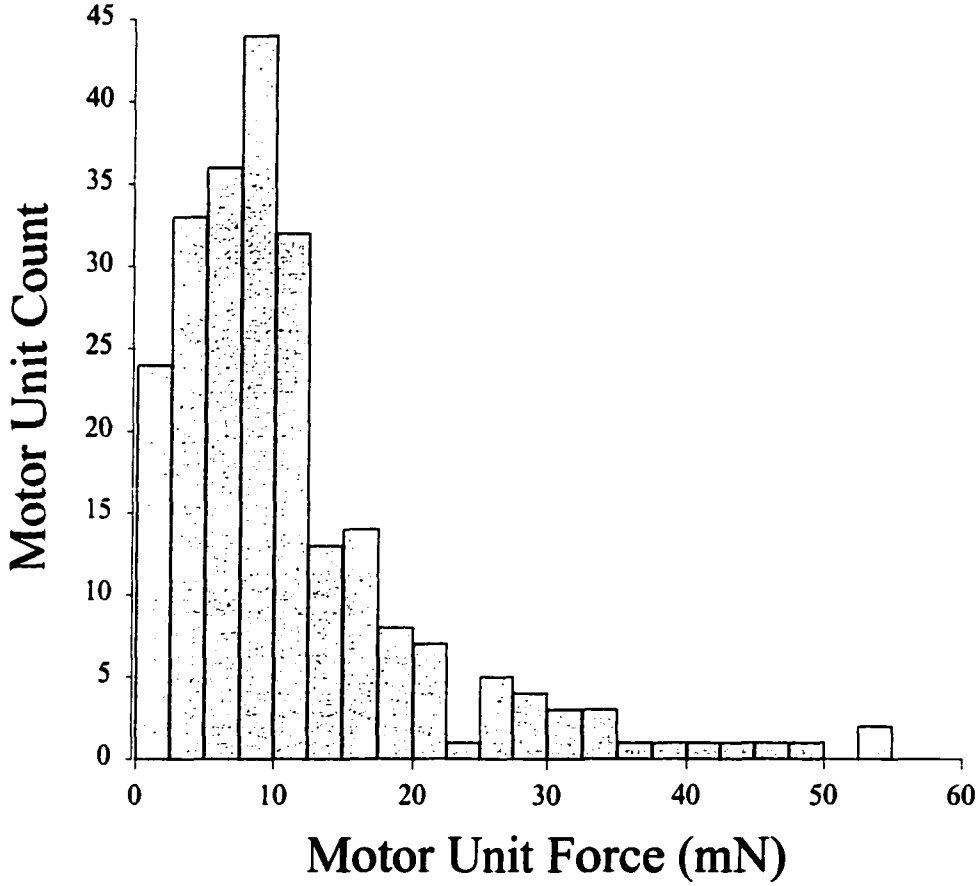

FIGURE 3.4 Distribution of 233 ED motor units according to the total force exerted on the four fingers. The majority of units produced low forces and few units generated large forces. The mean and median force for this sample was 11.4 ± 9.7 mN and 8.9 mN, respectively.

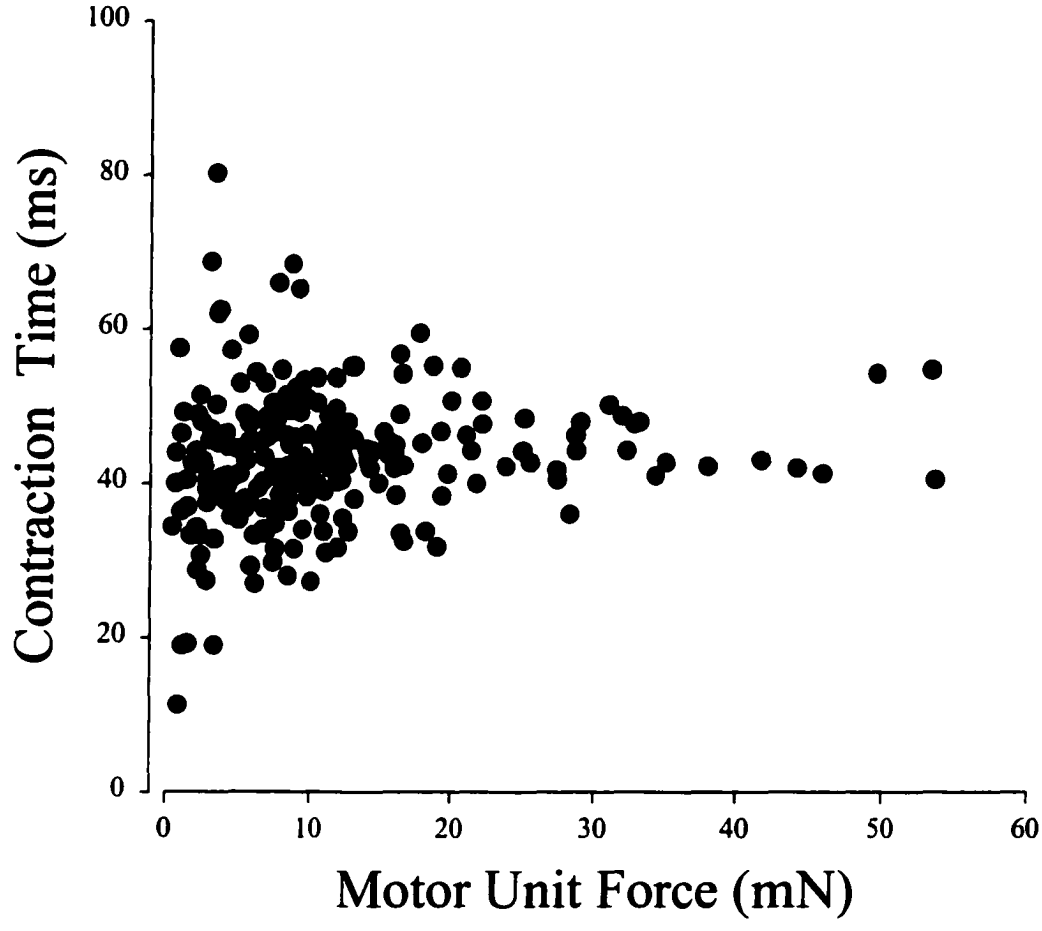

FIGURE 3.5 Relation between motor unit force and contraction time for 233 ED motor units. The mean contraction time for this population of motor units was 43.2 ± 8.6 ms. There was no correlation between motor unit force and contraction time.

tested produced force selectively on a single digit as would be expected for a muscle comprised of distinct functional compartments (Figure 8A). Therefore, the functional quantum by which the nervous system regulates force, the motor unit, does not appear to be dedicated to individual digits in ED. This result is surprising given the dexterity of the human hand and the relatively focused force for single motor units reported in the human flexor digitorum profundus by Kilbreath et al. (2002).

Studies in monkeys and in cats (Fritz et al. 1992; Schieber et al. 1997) have also shown that motor units in multi-tendoned muscles do not appear to produce force selectively on individual tendons. Fritz and colleagues (1992) showed that the force distribution of motor units in the cat extensor digitorum communis and extensor carpi ulnaris is broadly distributed with mean selectivity indexes of 0.14 and 0.28, respectively. Interestingly, Schieber and colleagues (1997) found the distribution of motor unit force in cat extensor digitorum lateralis to be more focused (mean selectivity index 0.68) than its homologous muscle extensor digiti quarti et quinti in the macaque monkey (mean selectivity index 0.57). Therefore, the degree of dexterity possessed by an animal may not necessarily correspond to the selectivity of motor unit force for individual digits.

There are at least three factors that may contribute to the apparent broad distribution of motor unit force across the fingers found in the present study. Synchronously active motor units may contaminate the twitch profiles obtained by spike-triggered averaging (Milner-Brown et al. 1973c). Our finding that motor unit force in ED was widely distributed across the fingers might be partially explained by some degree of synchrony in the discharge of motor units located in different compartments of ED (Figure 8B).

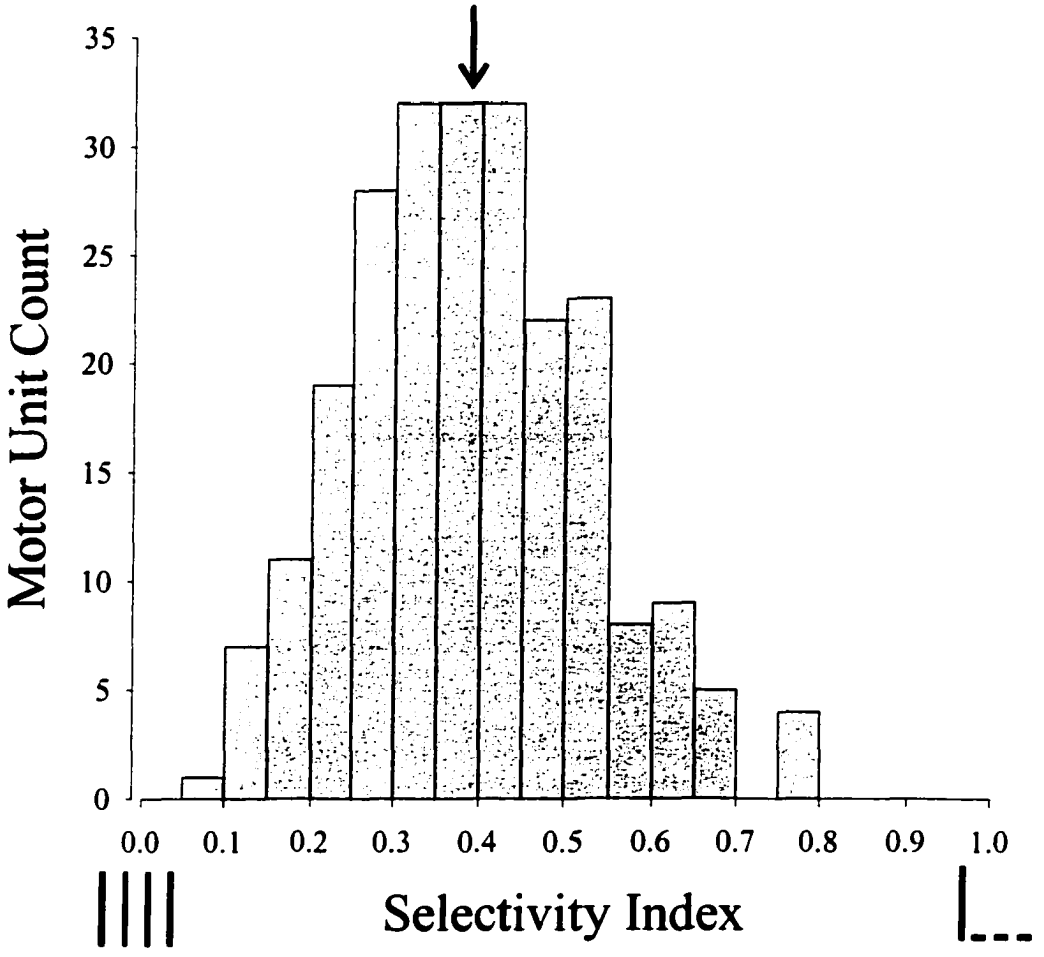

FIGURE 3.6 Distribution of ED motor units according to the selectivity index. The mean selectivity index for this population of 233 motor units was 0.38 ± 0.14 (arrow) indicating that spike-triggered average force in ED motor units is broadly distributed across the digits. A unit that contributed all its force to only one digit was never observed. The icons below the selectivity index values of 0.0 and 1.0 symbolize an even distribution of force, (i.e., four vertical bars representing the four fingers) and force focused entirely on one digit, respectively.

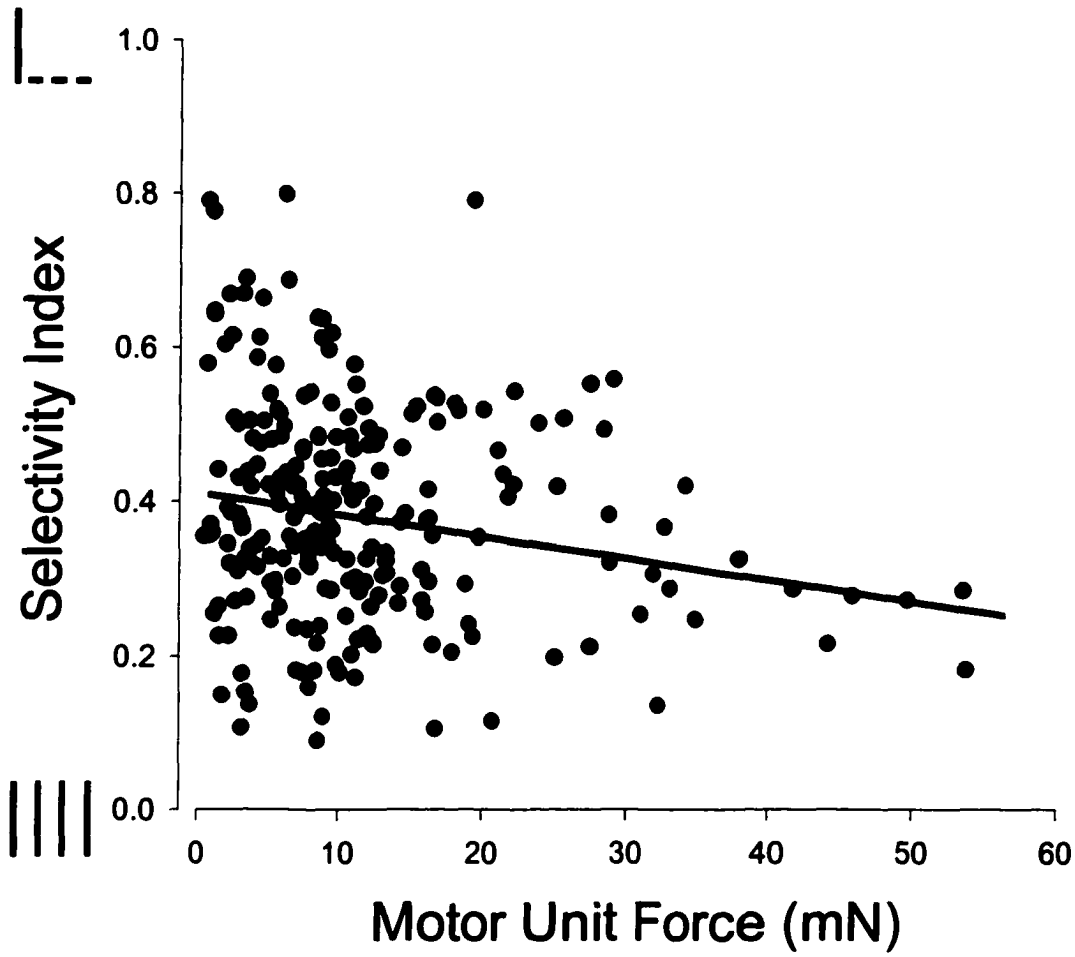

FIGURE 3.7 Plot of total motor unit force as a function of selectivity index for 233 ED motor units. There was a significant correlation between motor unit force and selectivity ($P = 0.003$). The stronger units tended to have slightly lower selectivity indices. Regression line shown is for this significant correlation which had a negative correlation coefficient of ($r = -0.19$).

Therefore, a study to determine the extent to which motor units in different compartments of ED discharge synchronously is required. This issue is addressed in chapter 5 of this dissertation.

The broad distribution of motor unit force could also be due in part to linkages between the distal tendons of ED that may cause the force developed in a single compartment to be transmitted to neighboring tendons (Figure 8C) (Balice-Gordon and Thompson 1988; Fritz et al. 1992). One way to determine the extent to which the broad distribution of motor unit force is due to the distal connections between tendons of ED would be to electrically stimulate the muscle fibers of a single compartment of ED. If distal linkages between tendons contribute significantly to the distribution in force across the fingers, then direct electrical stimulation of muscle fibers within one compartment of ED should result in force being developed on more than one finger. Conversely, if intertendonous connections play only a small role, then direct muscle stimulation of fibers within one compartment of ED should result in force being developed on a single finger. The results of this approach are described in detail in chapter four.

A third factor that might contribute to the force of motor units being broadly distributed across the fingers is that single motor axons supplying ED may branch extensively and innervate muscle fibers in multiple compartments (Figure 8D). It has been demonstrated using glycogen depletion in single-tendoned muscles in the rat and cat that motor unit territories can be extensive (Burke and Tsairis 1973; Tötösy de Zepetnek

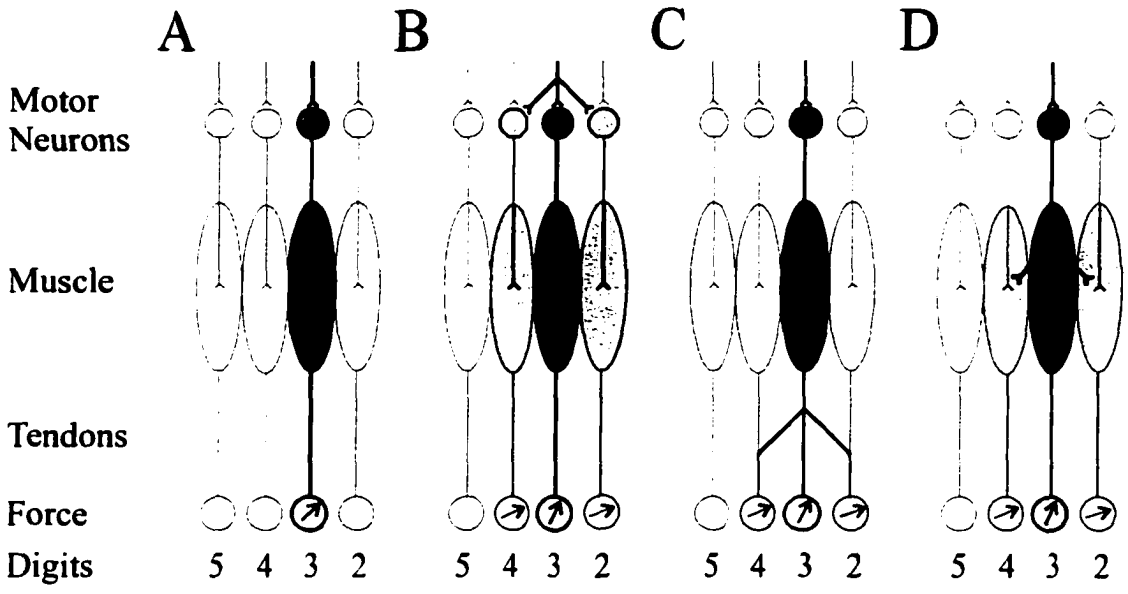

FIGURE 3.8 Schematic diagram depicting a functionally compartmentalized muscle and possible factors contributing to distribution of force across multiple tendons of the muscle. Ellipses represent different compartments of the muscle. The darker the symbol, the greater the relative activity of the motor neuron or muscle compartment. A) Each compartment is innervated by a separate set of motor neurons and each compartment exerts force on a single tendon providing independent control of the digits. B) Descending input to motor neurons supplying one compartment has branches that supply neurons innervating other compartments. Motor neurons innervating neighboring compartments will be active to some degree when attempting to activate a single compartment and the activity of motor units in one compartment may be correlated with motor units in other compartments. C) Connections between distal tendons cause some force to be transmitted from the active compartment to neighboring tendons. D) Muscle fibers supplied by single motor axons are not confined to a single compartment thereby causing force to be exerted on more than one tendon.

et al. 1992b). The extent to which the terminal distribution of motor axons contributes to the broad distribution of motor unit force can be tested using intraneural microstimulation of single motor axons that innervate ED. If the innervation of ED motor units is confined to individual compartments, then stimulation of single motor axons should result in selectivity index values compatible with those obtained with intramuscular stimulation. Alternatively, if intraneural microstimulation results in a broad distribution of force across the fingers, then this would indicate extensive branching of motor axons across compartments of ED. A full description of this study using this approach is presented in chapter six.

Given the apparent absence of independent actuators for each digit, as shown in this study and by others (Fritz et al. 1992; Schieber et al. 1997), extension of a single finger might require the co-activation of many muscles to prevent unwanted motion in other fingers and joints. Indeed, individuated finger movements in monkeys (Schieber 1995) and in humans (Rose et al. 1999) involve a complex array of muscles, including many considered as antagonistic to the specified movement. Even extension of digit 2 or digit 5 requires activation of a large number of hand muscles despite the existence of single-tendon muscles that extend digit 2 (extensor indicis) and digit 5 (extensor digiti minimi) alone (Rose et al. 1999). Consequently, it is possible that extension of an individual digit is not accomplished by the selective activation of a single muscular compartment in ED but rather by the co-activation of several agonist and antagonistic muscles.

CHAPTER 4

INTER-TENDONOUS CONNECTIONS PLAY A MINOR ROLE IN THE BROAD DISTRIBUTION OF MOTOR UNIT FORCE IN EXTENSOR DIGITORUM

INTRODUCTION

Extensor digitorum (ED) is the primary finger extensor muscle and gives rise distally to multiple tendons that insert onto all of the fingers. The spike-triggered average force of motor units in ED was found to be broadly distributed across many tendons (Keen et al. 1998). This observation suggests that significant coupling of finger movements might occur when attempting to extend a single finger. Indeed, studies that have measured the relative independence of finger movements in humans (Robinson and Fuglevand 1999; Häger-Ross and Schieber 2000) and monkeys (Schieber 1991) have found that fingers do not move independently of one another.

Why primates are unable to produce independent finger movements is not entirely clear. One possibility is that the juncturae tendinum, a system of lateral connective tissue bands between the distal tendons of ED, may distribute force from one tendon to the others (Forbes 1991). Such a mechanism of force dispersion across neighboring tendons may result in coupled movements of multiple fingers. Accordingly, surgical removal of the distal inter-tendonous connections of the junctuae tendinum might be expected to increase the ability to produce independent finger movements. Surgical resection of the juncturae tendinum, however, has produced mixed results. Removal of the juncturae tendinum surrounding the fourth digit in pianists (Forbes 1991) has been reported to be successful in improving independent extension of this finger. Conversely, sectioning of the juncturae tendinum has been reported to have no effect on the individuation of finger extension (Kaplan 1959).

Therefore, it is unclear if tension developed in a single compartment of ED is transmitted to neighboring tendons via distal inter-tendonous connections. If distal linkages between tendons are responsible for the broad distribution of motor unit force, then stimulation of muscle fibers confined to a single compartment of ED should cause force to be exerted on more than one finger. Alternatively, if the juncturae tendinum does not play a major role in distributing force across tendons, then intracompartmental stimulation should produce force primarily on one finger. Therefore, the purpose of this study was to determine the extent to which the distal connections between tendons of ED distribute force across the fingers.

METHODS

Fourteen experiments were performed on the right ED muscle in 4 healthy human volunteers (2 female, 2 male, ages 22-40 years). The experimental procedures were approved by the Human Investigation Committee at the University of Arizona. All subjects gave their informed consent to participate in the study. The experimental set-up was identical to that described in the previous chapter and therefore is only briefly summarized here. Subjects were seated with their right elbow and wrist supported and immobilized with the forearm held in a semi-supinated position. The wrist was stabilized by padded vertical posts placed on either side of the distal forearm and the dorsal and palmer aspects of the hand. The fingers were flexed at a right angle at the metacarpophalangeal joints and maintained in this position by metal cuffs around the proximal interphalangeal joints that were attached to separate force transducers via light-

weight cables. The length of each cable was adjusted at the beginning of the experiment so that each digit was preloaded in this flexed position with a force of approximately 2 N.

Force recording

Extension force of the digits was measured by four force transducers (Grass Instruments, Warwick, Rhode Island, model FT-10, range 0 – 5 N, sensitivity 780 mN/mV) mounted in a custom built manipulandum. Each transducer was aligned with the proximal interphalangeal joint of the appropriate finger. The force signals were amplified (X 1000) (World Precision Instruments, Sarasota, Florida) and displayed on an oscilloscope.

Stimulation

A tungsten microelectrode (Frederick Haer & Co. Bowdoinham, Maine, 1- to 5-μm tip diameter, 250-μm shaft diameter, ~ 4 kΩ impedance at 1000 Hz) with 2 to 3 mm of insulation removed from the tip, was inserted into ED to stimulate small bundles of muscle fibers. Stimuli consisted of 1 ms duration constant current pulses delivered at 1 pulse/s for 90 s (World Precision Instruments, Sarasota, Florida, Stimulus Isolator, model A365). To minimize current spread to neighboring compartments or to motor axons, stimulus intensity was adjusted to be slightly greater than the minimal current necessary to elicit a force response (usually between 0.1 and 0.3 mA). Because the threshold for activation of nerve branches is much lower than muscle fibers (Mortimer 1981; Hultman et al. 1983), we initially stimulated in the distal third of the muscle. It is likely that the motor end plate region is restricted to a narrow band at a proximal or mid muscle level (Aquilonius et al. 1984). Therefore, the distance from the distal stimulation sites to

motor axons innervating ED was probably at least 2 cm. Based on estimates of the current necessary to excite nerve fibers at different distances from the source (Mortimer 1981), stimulation of motor axons innervating ED would have required several orders of magnitude greater current than was delivered. After stimulation at one site, the electrode was reinserted 2-5 mm lateral to the previous site. This process was repeated to sample the entire medial-lateral extent of ED. In separate experimental sessions, the distal, middle and proximal regions of ED were tested. Each site was marked with a small ink dot after removal of the electrode. Following the experiment, a feduciary mark was placed on the lateral epicondyle of the humerus and styloid process of the ulna. The subject then held their right arm in a semi-pronated position with the elbow flexed at a right angle and was photographed using a digital camera.

Data Analysis

Extension force of each finger and current pulses were digitally sampled at approximately 2.5 and 20 kHz, respectively, using the Spike2 data acquisition and analysis system (Cambridge Electronics Design, Cambridge, England). Data were analyzed off-line using Spike2 and custom designed software. Stimulus pulses were used as triggers to send brief segments (140 ms, 15 ms pre-trigger) of each force channel to an averaging algorithm (Stein et al. 1972; Stephens and Usherwood 1977). The resulting stimulus-triggered average of each force channel provided an estimate of the electrically-evoked force developed on each finger. Total force for each stimulation site was calculated as the sum of the peak stimulus-triggered average force across all fingers. Unweighting of preloaded flexion force was treated as a negative force.

A selectivity index (Schieber et al. 1997) was used to quantify the distribution of force in response to electrical stimulation at each site across the four fingers. Calculation of the selectivity index was described in the previous chapter. Conceptually, a selectivity index of 1.0 represents a site where stimulation transmitted all of its force to one finger, whereas a selectivity index of 0.0 indicates a stimulation site in which evoked force was evenly distributed across the fingers. A preferred finger was designated for each stimulation site based on the digit to which the stimulation produced the most force.

Analysis of variance was used to compare the selectivity index between preferred fingers and between proximal, middle and distal stimulation sites. A Student's t-test was used to compare selectivity index values obtained by electrical stimulation and spike-triggered averaging of single motor units. Values are reported as means ± standard deviation with a probability of 0.05 selected as the level of significance.

RESULTS

The force distribution across the four fingers for 107 different sites of electrical stimulation in human ED is reported in this chapter. An average of 7.6 ± 2.6 different sites were tested per experimental session. A sample recording of approximately 8 seconds extracted from a 90 second record is shown in Figure 1. The top trace shows the delivery of a stimulus pulse at a frequency of 1 Hz. The lower four traces from the bottom up are the force recordings for digits 2 through 5 (index, middle, ring, and little fingers, respectively). Force transients associated with the stimulus pulse are evident on the traces of the third and fourth digits. An arterial pulse-pressure artifact at a frequency of approximately 1 Hz is evident on each of the force traces but is not temporally

associated with the stimulus pulse. Stimulus-triggered averaging of the four force channels was utilized to obtain an estimate of the force exerted by stimulation on each finger. The average number of current pulses delivered at each site was 96.5 ± 10.2 (range of 74 to 139) with an average current of 201.1 ± 125.5 μA (range of 30 to 600 μA).

Examples of the stimulus-triggered average force developed on each finger are shown in Figure 2 from four sites with different preferred fingers (D2 through D5, Figs 2A, 2B, 2C,and 2D, respectively). The four sites in Figure 2 had selectivity index values of 0.73, 0.70, 0.74, and 1.1 and produced a total force of 55.3 mN, 118.9 mN, 130.3 mN and 90.8 mN (Figs 2A-D, respectively). These sites exhibited a more focussed force distribution compared with the spike-triggered average forces of single motor units. A slight unloading of digits 3 and 4 can be seen in Figure 2D. Consequently, these fingers were assigned negative force values which resulted in a selectivity index greater than 1.0.

The electrode was repeatedly removed and reinserted as many as 13 times in a given experimental session (Figure 3). Each vertical row of dots in Figure 3 represents the insertion sites for a single experiment. The four bar icons at the right of the figure represent from top to bottom, the relative amount of force produced on digits 2 – 5 respectively. An experiment was terminated when the electrode repeatedly failed to elicit a response in ED or elicited a response in extensor carpi radialis. The mean total force for all 107 sites tested was 120.6 ± 88.4 mN with a range from 680.9 to 21.5 mN. Two adjacent sites yielded unusually large forces of 550 and 680 mN focussed on D3 in response to relatively small currents of 60 and 100 μA, respectively. A primary nerve

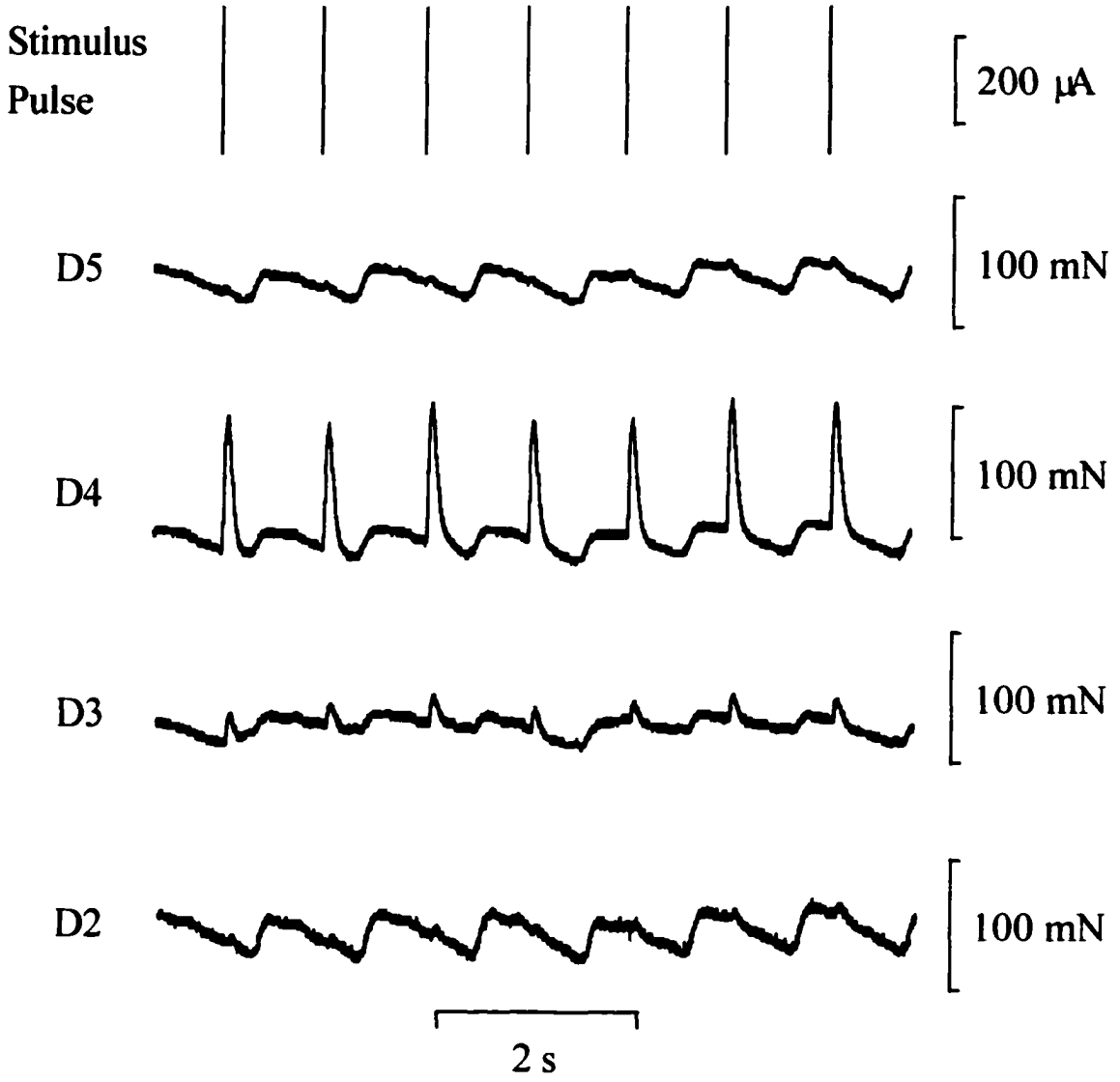

FIGURE 4.1 Brief sample of data extracted from a ninety-second trial of direct muscle stimulation of a bundle of muscle fibers in ED. The stimulus pulses are shown at the top and force traces for the four fingers below. The stimulation resulted in most of the force being produced on D4. Force transients not temporally associated with the stimulus pulse are an arterial pulse-pressure artifact.

branch innervating the D3 compartment may have been activated directly at these two sites. Both sites had relatively high selectivity indexes of 0.88.

Force Distribution

The distribution of force in response to intramuscular stimulation of small bundles of muscle fibers across the four digits was quantified using a selectivity index derived by Schieber et al. (1997) (see Methods). The mean selectivity index for all sites tested was 0.70 ± 0.21 with a range from 0.31 to 1.52. These selectivity index values were significantly greater ($P<0.001$) than those obtained for single motor units using spike-triggered averaging (Keen et al. 1998). This difference is evident in Figure 4, which compares the selectivity indexes of spike-triggered average motor unit force and electrical stimulation of ED. Both histograms have been normalized to the number of observations in each study. Arrows indicate the mean values from the two studies.

All subjects participated in 3 experiments in which the electrode was positioned distally, at a mid-level and proximally along the length of the muscle (Figure 3). Interestingly, there was a significant difference in the selectivity index between the three different proximal to distal stimulation locations in ED (Figure 5). The selectivity index in the middle of the muscle was significantly smaller (i.e., a broader force distribution) with a mean selectivity index of 0.59 ± 0.18 compared with the distal or proximal sites ($P < 0.001$). There was no difference in the selectivity index between the proximal and distal sites, which yielded selectivity indexes of 0.75 ± 0.1 and 0.8 ± 0.26, respectively. There was not a significant difference in the amount of current delivered between the proximal, midlevel and distal sites. It is unclear why sites in the middle of the muscle

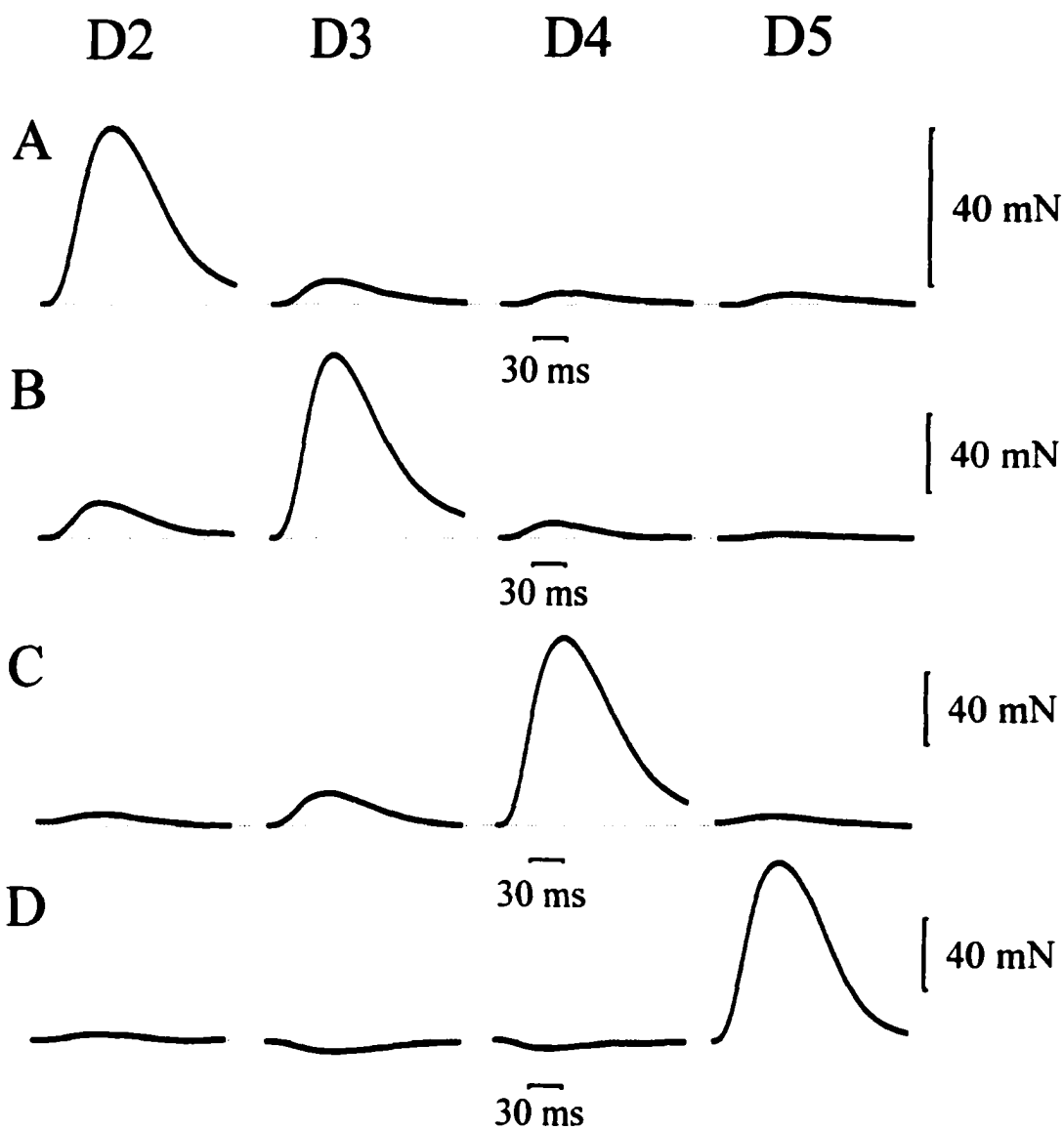

FIGURE 4.2 Examples of the stimulus-triggered average forces evoked by direct muscle stimulation from four different sites. Stimulation at each of these sites evoked force primarily on a single finger. Stimulation sites were categorized based on the digit in which the greatest force was produced. These sites were categorized to have D2 (A), D3 (B), D4 (C), and D5 (D) as preferred fingers with selectivity index values 0.73, 0.70, 0.74, and 1.1, respectively. Occasionally, unloading was observed and is shown for D3 and D4 in D.

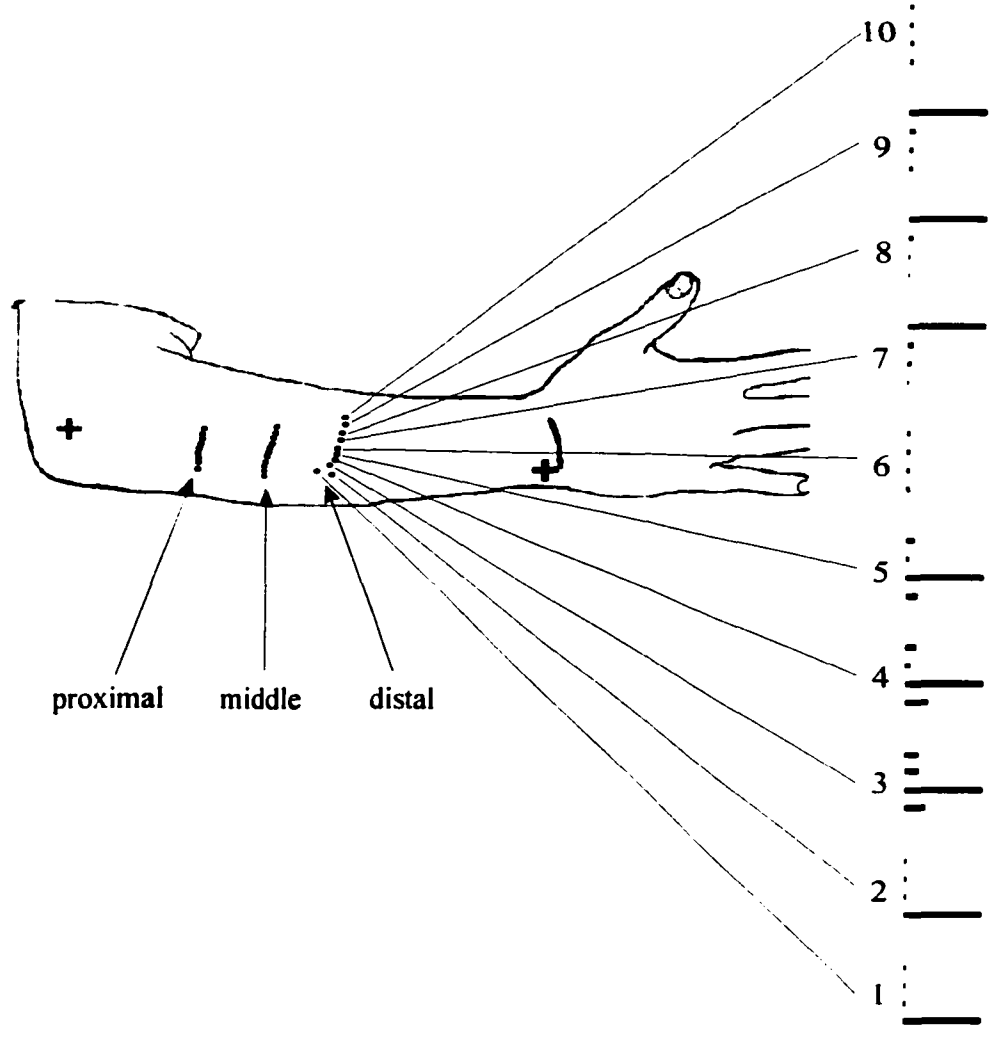

FIGURE 4.3 Insertion sites (small dots) of tungsten microelectrode into ED at a proximal, middle and distal level and the corresponding force developed on all four fingers at distal sites for one subject. Each four-bar icon at the right represents, from top to bottom, the relative amount of force produced on digits 2 - 5, respectively, during direct muscle stimulation. No detectable force was elicited at site 6 or site 10. The plus symbols are feduciary marks indicating the location of the lateral epicondyle of the humerus and styloid process of the ulna.

were less selective.

There was also a significant difference of the selectivity index across preferred fingers. Those sites that elicited more force on the little finger had higher selectivity ($P < 0.001$) than any of the other three fingers (Figure 6). The mean selectivity indexes for digits 2 through 5 were 0.75 ± 0.11, 0.64 ± 0.17, 0.63 ± 0.11, and 0.99 ± 0.24, respectively. Interestingly, six sites produced selectivity index values greater than one. The fifth digit was the preferred finger for each of those sites. A value greater then one was obtained when adjacent fingers were unloaded (negative force) by the stimulus (Figure 2D). Unloading of the neighboring fingers was observed in all four subjects.

DISCUSSION

The objective of this experiment was to determine the extent to which the distal linkages among the tendons of ED transmit force across the tendons. If the juncturae tendinum play a significant role in distributing force across multiple fingers, then an appreciable amount of force should have been directed to other digits with direct stimulation of muscle fibers within a compartment. However, force arising from intramuscular stimulation of contiguous bundles of muscle fibers in ED was significantly more focused on a single finger compared with spike-triggered average motor unit force. This finding suggests that intertendonous connections account for only a modest part of the broad distribution of motor unit force observed in ED.

Two factors may have contributed to slight underestimates of the actual selectivity in this study. First, the stimulating microelectrode was moved laterally in small steps across the extent of ED. Undoubtedly, this resulted in the electrode being positioned at least

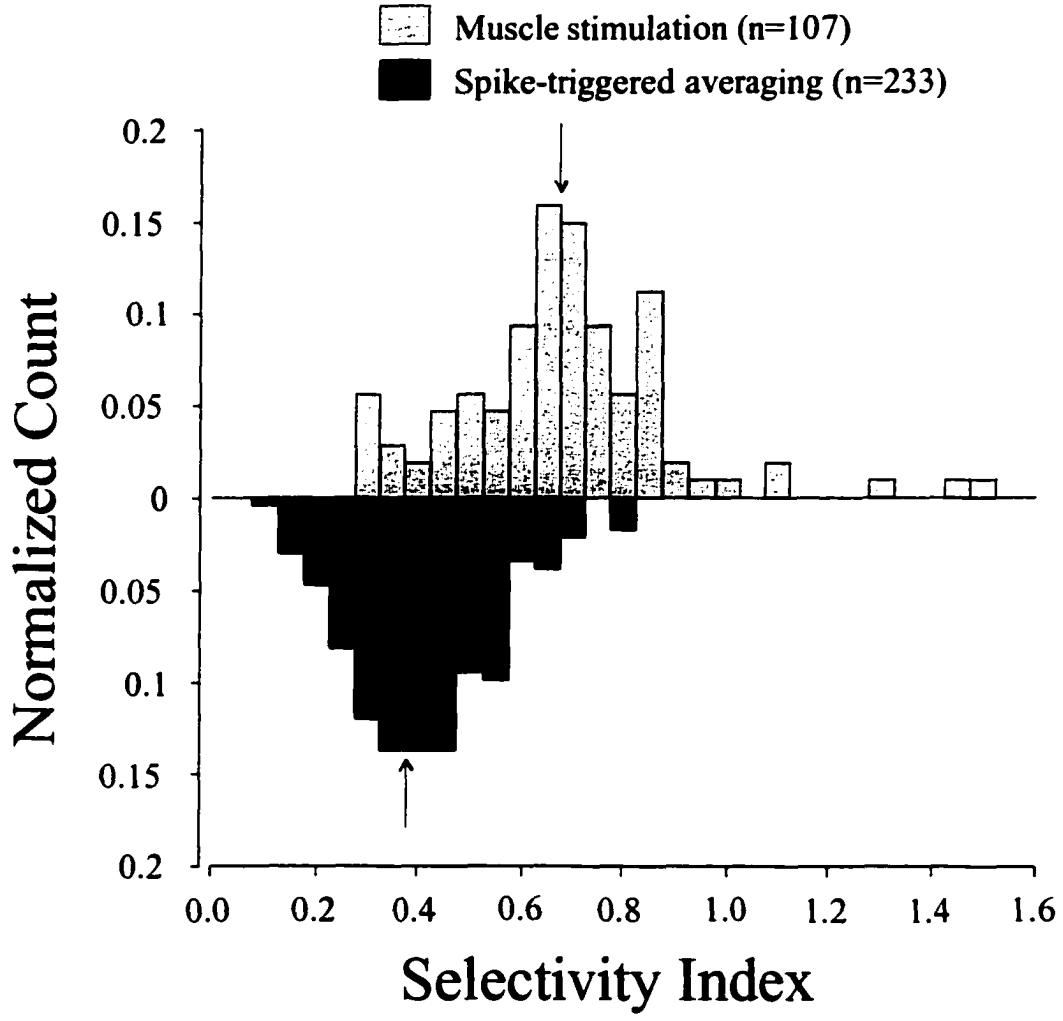

FIGURE 4.4 A comparison of selectivity index based on responses evoked by intramuscular stimulation of ED to spike-triggered averages of ED motor units. Spike-triggered average force in 233 ED motor units was broadly distributed across the fingers with a mean selectivity index of 0.38 ± 0.14. Direct stimulation muscle fibers in ED yielded a higher mean selectivity index of 0.7 ± 0.2. Arrows indicate the mean values for each study.

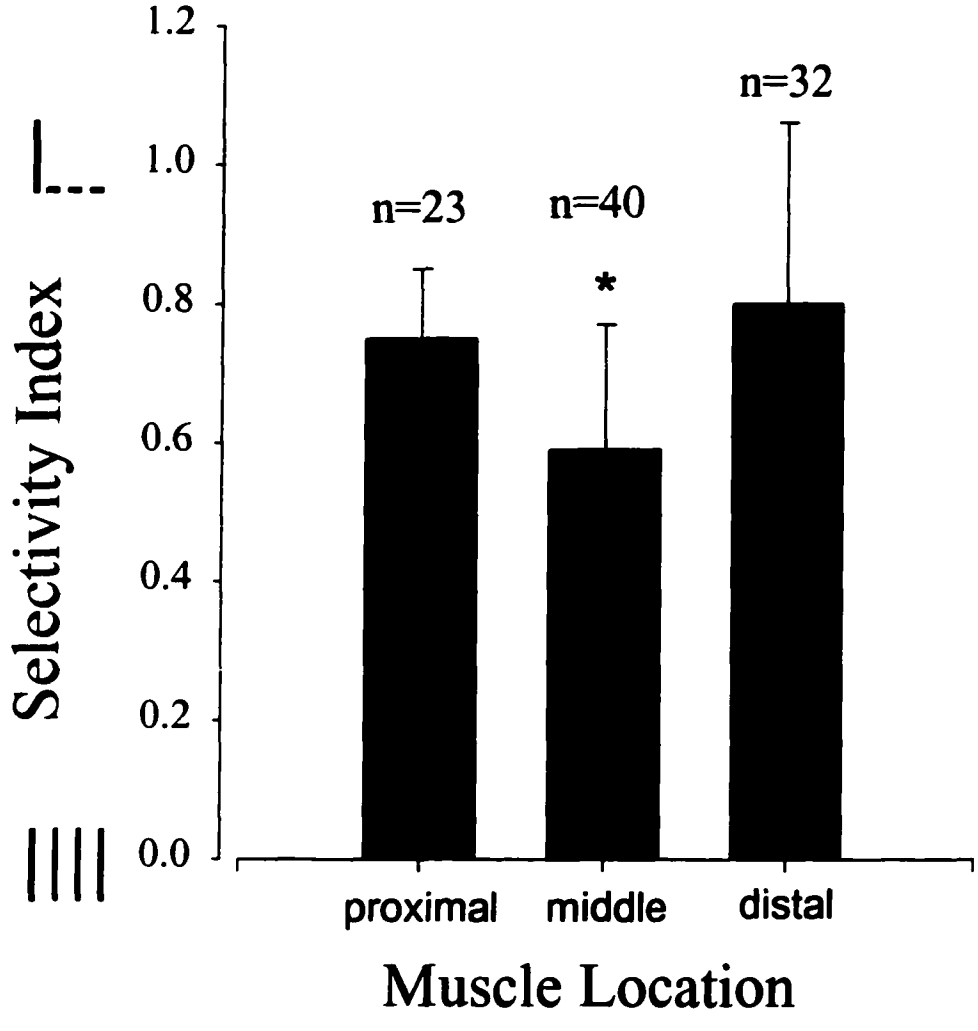

FIGURE 4.5 Mean (±SD) selectivity index for sites at proximal, middle or distal locations in ED. The number of sites at each location is shown. Intramuscular stimulation at middle sites evoked significantly lower selectivity values than proximal or distal sites. The icons beside the selectivity index values of 0.0 and 1.0 symbolize a uniform distribution of force and force focused entirely on one digit, respectively.

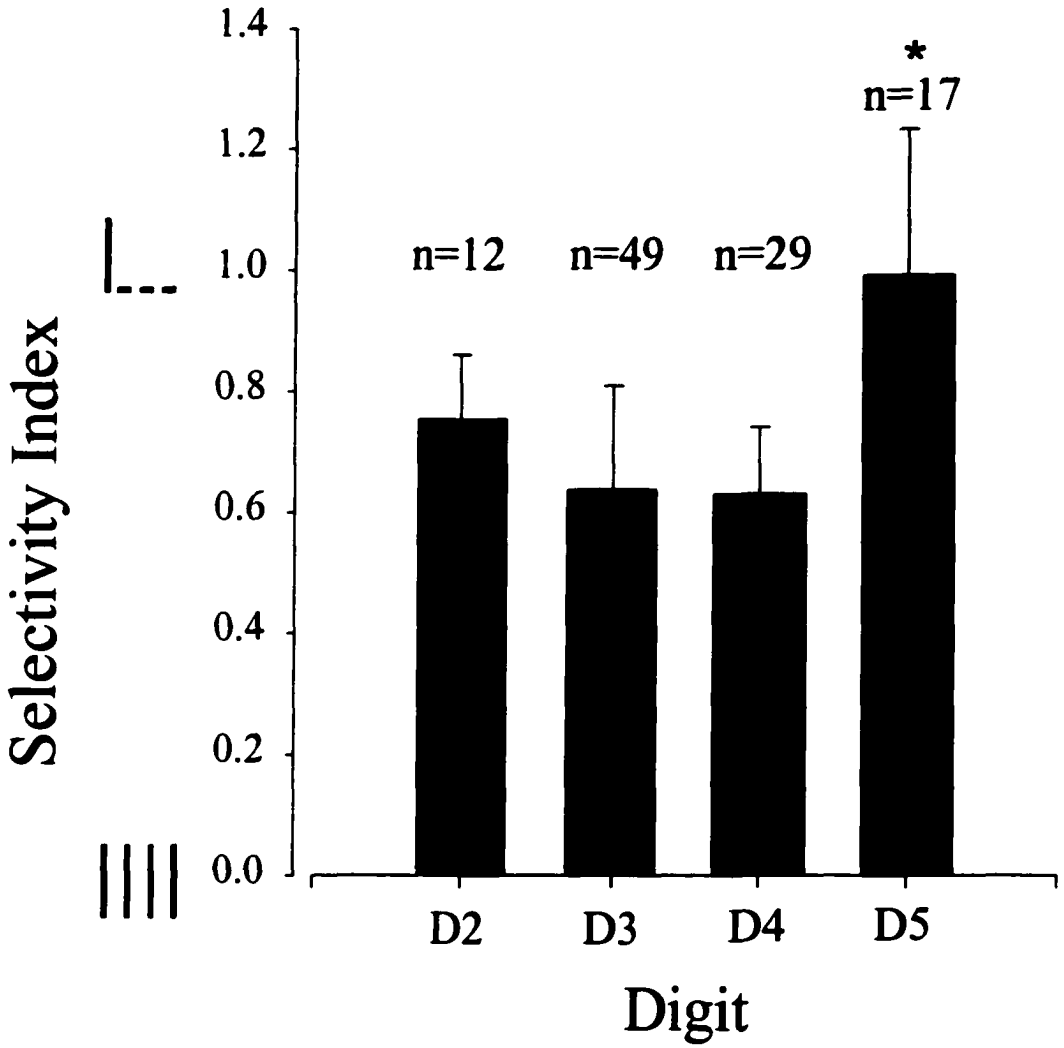

FIGURE 4.6 Mean (±SD) selectivity index for each preferred finger. Stimulation sites were categorized based on the digit in which the greatest force was produced. The number of sites for each finger is shown. The fifth digit had a significantly higher selectivity index than the other three fingers (indicated by the astrix above D5). The icons beside the selectivity index values of 0.0 and 1.0 symbolize a uniform distribution of force and force focused entirely on one digit, respectively.

occasionally on a boundary between neighboring compartments. Consequently, at these sites, stimulation may have activated muscle fibers belonging to two compartments.

Second, it is probable that electrical stimulation occasionally excited nerve branches when the electrode was in the vicinity of motor axons. This is likely because the threshold for activation of nerve branches is much lower than muscle fibers (Mortimer 1981; Hultman et al. 1983). Consequently, retrograde propagation and invasion of the action potential down nerve branches may have activated entire motor units. Muscle fibers comprising a single motor unit usually are dispersed over a broad region of the cross section of single-tendoned muscles (Burke and Tsairis 1973; Tötösy de Zepetnek et al. 1992b). Therefore, muscle fibers in multiple compartments that belonged to single motor units may have been activated by electrical stimulation leading to lower selectivity index values not attributable to the distal connections between tendons of ED. Consequently, the extent to which the juncturae tendinum distribute force across the fingers was probably overestimated in this study.

To determine the extent to which inter-tendonous connections distribute force across the fingers at a whole muscle level, direct stimulation of primary nerve branches supplying different compartments of flexor digitorum profundus was performed in the macaque (Schieber et al. 2001). Although stimulation selectively activated individual compartments, the selectivity index values were relatively low. They concluded that the inter-tendonous connections in the macaque are responsible for the distribution of force across the fingers. However, in the macaque, the tendons of flexor digitorum profundus are heavily inter-connected and do not clearly separate into individual tendons inserting

onto each finger until the level of the palm (Schieber et al. 2001). In humans, the tendons of ED are distinct by the distal third of the forearm (Kaplan 1959) and are not as heavily inter-connected as in the macaque.

The juncturae tendinum between the distal tendons of ED in humans has been carefully examined and categorized into three types (von Schroeder et al. 1990). Type 1 consists of tiny filamentous bands of connective tissue predominantly found between the tendons of D2 and D3 and to a much lesser extent between D3 and D4. They most often have a transverse orientation between the two tendons they attach. Type 2 and type 3 juncturae tendinum are only found in the inter-tendonous spaces surrounding D4. The type 2 juncturae tendinum is thicker than type 1 and attaches more proximally on the tendon of the fourth digit compared with the attachment on the tendons of the third or fifth digits. Type 3 juncturae tendinum resemble split tendons that insert into adjacent fingers. These three types of juncturae tendinum have been suggested to serve a variety of functions including maintenance of appropriate spacing between ED tendons (Brand 1985), coordination of extension (Boyes 1970), and stabilization of the metacarpophalangeal joints (Agee and Guidera 1980). Indeed, several investigators have found that the juncturae tendinum may prevent independent extension of the fingers. Surgical removal of the juncturae tendinum has been found to increase the independence of finger extension movements in pianists (Forbes 1991). Also, removal of the juncturae tendinum and web between the fingers in cadaver hands results in more fractionated finger extension movements when tension is applied to individual tendons (von Schroeder and Botte 1993). Furthermore, modeling work suggests that surgical resection

of the junturae tendinum may result in a greater independence of finger movements (Leijnse et al 1993). However, Kaplan (1959) found no difference in the independence of finger movements after removal of the juncturae tendinum. The results of the present study are consistent with the findings of Kaplan that the juncturae tendinum play only a minor role, in the dispersion of force across the fingers.

In summary, the intent of the current report was to determine if the distal connections between the tendons of ED in normal human subjects were responsible for a broad distribution in motor unit force, which might result in coupled finger movements. The force produced by electrical stimulation of ED was significantly more focussed on a single finger compared with the spike-triggered average force of single motor units. Consequently, inter-tendonous connections likely account for only a small part of the broad distribution of motor unit force observed in ED.

CHAPTER 5

CROSS CORRELATION ANALYSIS REVEALS MODEST DEGREE OF SYNCHRONY BETWEEN MOTOR UNITS IN DIFFERENT COMPARTMENTS OF EXTENSOR DIGITORUM

INTRODUCTION

A fundamental issue that underlies the coordination of activity among a population of neurons relates to the distribution of synaptic input. In an important set of studies, the proportion of motor neurons supplying a given muscle that received synaptic input from single afferent or descending axons were identified (Somjen et al. 1965; Mendell and Henneman 1971; Binder et al. 1996). The remarkable finding of these studies was that individual input fibers ramify to make synaptic contact with most (in many cases all) of the motor neurons comprising a motor nucleus. This observation of extensive divergence contributed to the idea that inputs are distributed in a roughly uniform way across a motor neuron population. Therefore, the primary determinate of recruitment susceptibility appears to be related in large part to intrinsic properties of the motor neurons (Henneman and Mendell, 1981). Furthermore, the concept of a motor neuron 'pool' representing an assembly of neurons that receive similar inputs and which control a single muscle derives in part from these experimental observations on synaptic input organization.

It is unclear, however, how to designate a pool of motor neurons in the context of a muscle that is subdivided into more than one part. One possibility is that the entire array of motor neurons that innervate a multi-compartment muscle receive more or less similar inputs. Control over different parts of the muscle, therefore, could be effected by differences in intrinsic properties between subsets of motor neurons, such as occurs for low and high threshold motor neurons supplying deep and superficial regions, respectively, of hind limb muscles in rodents (Kernell 1998). Alternatively, motor neurons supplying different parts of a muscle might receive relatively distinct synaptic

inputs. In this case, activation of different parts of a muscle (or subsets of motor units) would depend primarily on the input pathways engaged. Consequently, it was of interest to determine which of these fundamentally different organizational frameworks might operate to control a multi-tendon finger muscle like the human extensor digitorum (ED). Because it is not possible to measure directly synaptic input distribution in human subjects, we instead estimated the extent of divergence in last-order inputs to motor neurons by measuring the degree of short-term synchrony among motor units within and across compartments of ED (Sears and Stagg 1976; Kirkwood and Sears 1978; Nordstorm et al. 1992).

METHODS

Twenty-four experiments were performed on the right ED muscle in 9 healthy human volunteers (5 female, 4 male, ages 21-40 years). The experimental procedures were approved by the Human Investigation Committee at the University of Arizona. The experimental set-up was identical to that described in the previous two chapters and therefore is only briefly summarized here. Subjects were seated with their right elbow and wrist supported and immobilized with the forearm held in a semi-supinated position. The fingers were flexed at a right angle at the metacarpophalangeal joints and maintained in this position by metal cuffs around the proximal interphalangeal joints that were attached to separate force transducers via light-weight cables.

Force and EMG recording

Extension force of the digits was measured by four force transducers (Grass Instruments, Warwick, Rhode Island, model FT-10, range 0 – 5 N, sensitivity 780

mN/mV) mounted in a custom built manipulandum. The manipulandum allowed each transducer to be aligned both horizontally and vertically with the proximal interphalangeal joint of each finger. The force signals were amplified (X 1000) (World Precision Instruments, Sarasota, Florida) and displayed on oscilloscopes.

Motor unit action potentials were recorded with tungsten microelectrodes inserted into ED (Frederick Haer & Co. Bowdoinham, Maine, 1- to 5-μm tip diameter, 5- to 10-μm uninsulated length, 250-μm shaft diameter, ~ 200 kΩ impedance at 1000 Hz after insertion). Surface electrodes (4 mm diameter Ag-AgCl) attached to the skin overlying the radius served as reference electrodes for the intramuscular electrodes. Two microelectrodes were inserted at different locations in ED in order to record the activity of at least one motor unit on each electrode simultaneously. Electrical stimulation was used initially to verify placement of microelectrodes in target compartments of ED. The electrodes were then connected to differential amplifiers and the intramuscular electromyographic (EMG) signals were amplified (X 1000), band pass filtered (0.3-3 kHz) (Grass Instruments, Warwick, Rhode Island), and displayed on oscilloscopes.

Protocol

Subjects performed low force isometric extension of all four fingers to activate ED. The microelectrodes were gently manipulated during the contraction until action potentials of motor units could be clearly identified on each electrode. Once a different motor unit was identified on each electrode, subjects sustained weak contractions of ED such that both units remained active. Intramuscular EMG signals were recorded for three minutes or until the motor unit action potentials could no longer be clearly discriminated.

Subjects received visual and auditory feedback on the discharge of the motor units and 1-2 minutes of rest between recordings. After each recording, the position of at least one and often both of the microelectrodes was adjusted until the action potentials of a presumably different motor unit could be identified. This occasionally involved removal of a microelectrode and reinserting it at a new site. Successive trials were performed for up to two hours. Extension force of each finger and intramuscular EMG signals were digitally sampled at approximately 2 and 18.5 kHz, respectively, using the Spike2 data acquisition and analysis system (Cambridge Electronics Design, Cambridge, England).

Data Analysis

Data were analyzed using Spike 2 and custom designed software. Motor unit discrimination was accomplished using a template-matching algorithm based on waveform shape and amplitude. An event channel representing the timing of discharges of accepted action potentials for a motor unit was generated. The discharge times of one unit, termed the event unit, were plotted relative to the discharge times of a second unit, termed the reference unit to generate a cross-correlation histogram or cross-correlogram. Cross-correlation histograms had 1 ms bin widths and included periods of 100 ms before and after the discharge of the reference unit. A peak in the cross-correlation histogram around time zero represents the synchronous firing of the two units greater than expected due to chance (Nordstrom et al. 1992). The magnitude of the synchronous peak is thought to reflect the extent of shared last order inputs to the two neurons (Sears and Stagg 1976).

The cumulative sum procedure (cusum) was used to identify a synchronous peak in the cross-correlogram and was calculated by adding the successive differences between the count of each bin and the baseline mean (Ellaway 1978). The baseline mean (M) was calculated as the mean count in the first and last 60 ms of the cross-correlogram (Figure 1). A rise in the cusum near time zero was used to delineate a peak in the cross-correlation histogram. Specifically, peak boundaries were determined as the bins corresponding to 10% and 90% of the difference between the minimum and maximum cusum values (Schmied et al. 1993) (Figure 1). The magnitude of the peak in the cross-correlograms was quantified as number of counts within the boundaries of the peak (P) above the baseline mean (M) divided by the duration of the recording. This synchronization index, referred to as common input strength (CIS), indicates the rate of extra synchronous impulses (i.e., extra imp./s) above that expected due to chance (Nordstrom et al. 1992).

One problem of the cross-correlation technique has been in developing a consistent statistical test to differentiate between significant and non-significant peaks. A variety of different methods for detecting a significant peak have been proposed (Schmied et al. 1993; Stephens 1980; Davey et al. 1986; Wiegner and Wierzbicka 1987). Of these, we adopted the technique proposed by Schmied and colleagues (1993) where the significance of the cross-correlogram peak was determined by calculating the *z* score, namely, the average number of counts in the peak minus the average number of counts in the off-peak area divided by the standard deviation of the counts in the off-peak area. The *z* score reflects the number of standard deviations by which the mean count in the

peak exceeds the mean baseline count (Schmied et al. 1993). The peak was required to be greater than 3 standard deviations above the mean count in the off-peak (z score $\geq$ 1.96) to be considered significant. If the z score was not significant, 11 ms surrounding the discharge of the reference unit was used to calculate the CIS and this value was then included in the statistical analysis.

When both electrodes were confined to the same compartment of ED, the CIS values were referred to as being intra-compartmental. A one-way ANOVA was used to compare the intra-compartment CIS values across the four compartments. When the electrodes were located in different compartments of ED, CIS values obtained were referred to as being extra-compartmental. ANOVA was also used to determine differences in the degree of synchrony for the extra-compartmental comparisons. Tukey post hoc analysis was used to identify differences in CIS within intra- and extra-compartmental groups. A two-tailed Student's t-test was used to compare the CIS values for all intra-compartmental to all extra-compartmental recordings. Values are reported as means $\pm$ standard deviation with a probability of 0.05 selected as the level of statistical significance.

RESULTS

A total of two hundred and seventy two motor units in ED were recorded which were used to generate one hundred and forty five cross-correlation histograms. In seventeen trials, more than one unit was discriminated on an electrode which yielded multiple correlations. The mean firing rate for all recorded motor units was 10.6 $\pm$ 2.0 Hz and the mean number of events used to generate the cross-correlograms was 1864 $\pm$ 836. Four

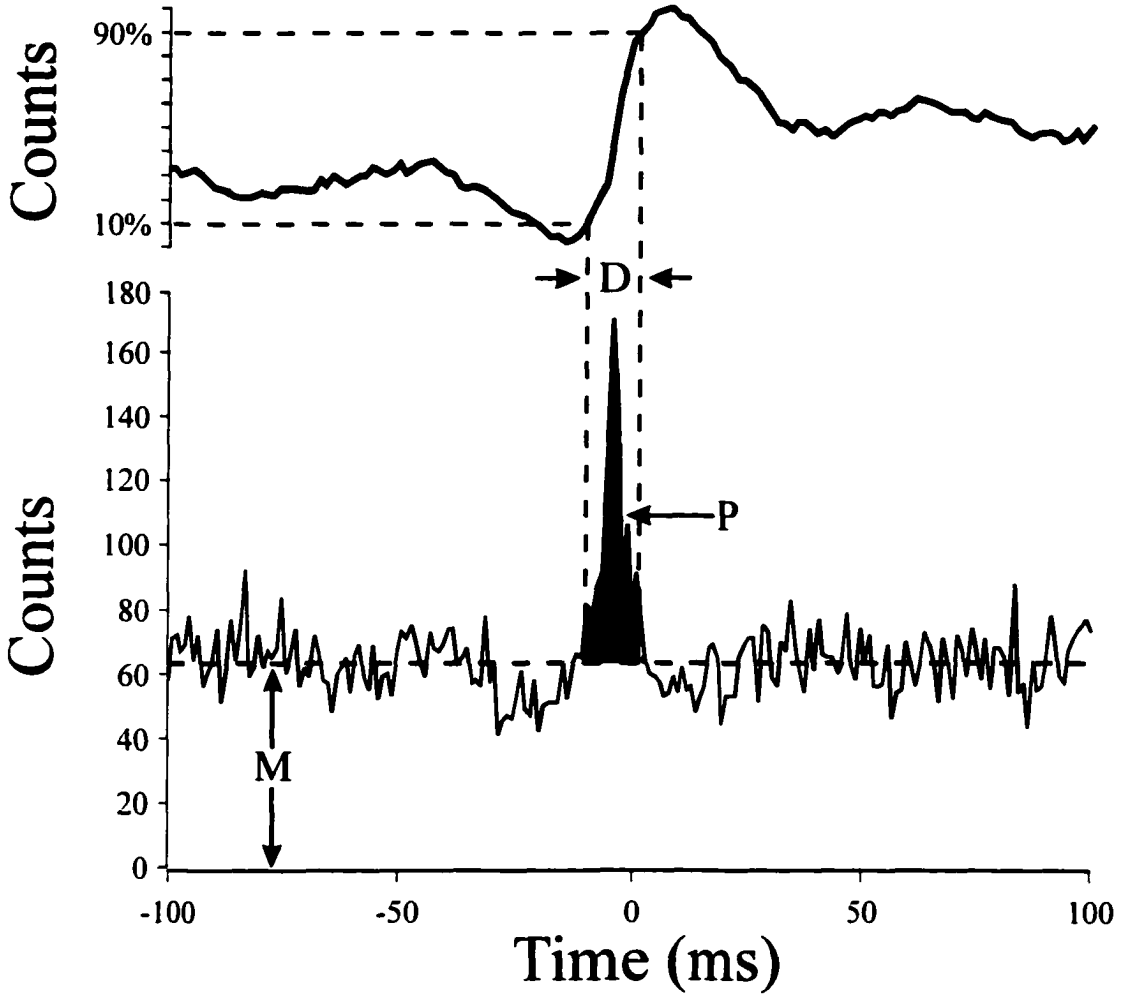

FIGURE 5.1 Cross-correlation histogram from a pair of motor units recorded in the digit 3 compartment of extensor digitorum to illustrate method to quantify synchrony. Upper trace shows the cumulative sum which was used to identify the duration (D) of the synchronous peak in the histogram. The mean bin count determined over the first and last 60 ms of the histogram is denoted as M. The value of M is used to distinguish those counts expected due to chance from those counts in excess of chance (area P) within the synchronous peak. The 10% and 90% difference between the minimum and maximum cusum values are denoted with dashed lines in the upper trace. The absolute values of the cusum ranged from approximately –200 to 300 counts.

examples of cross-correlograms are shown in Figure 2. The labels at the top of the figure indicate the compartments that each of the microelectrodes was located within. Substantial synchrony was found for the pair of units both located in the D3 compartment with a CIS of 0.76 (Figure 2B). A significant degree of synchrony was also observed for a D3 – D4 pair of units with a CIS of 0.63 (Figure 2C). However, little synchrony was found when the two electrodes were in non-adjacent compartments i.e., D3-D5, (Figure 2D) or in the neighboring compartments of D2 and D3 (Figure 2A) with CIS values of 0.22 and 0.28, respectively.

The duration of the synchronous peak, assessed from the cusum, was on average 12.6 ± 5.2 ms for all cross-correlograms. The mean CIS values for all motor unit pairs recorded both within and across compartments is shown in Figure 3. Eighty motor unit pairs in total were recorded from within the same compartment (solid bars, Figure 3). These had mean CIS values of 0.54 ± 0.14 (n = 24), 0.66 ± 0.28 (n = 23), 0.9 ± 0.39 (n = 21), and 0.75 ± 0.2 (n = 12) for D2 through D5 compartments, respectively. A one way ANOVA revealed a significant difference between compartments in the CIS values for intra-compartment motor unit pairs ($P<0.001$). A Tukey post-hoc analysis revealed that the CIS values for motor unit pairs within the D4 compartment were significantly greater than for motor unit pairs within the D2 compartment. No other intra-compartment comparisons were significant.

Sixty-two motor unit pairs were recorded that resided in neighboring compartments of ED. The mean CIS values for extra-compartmental groups were 0.20 ± 0.13 for

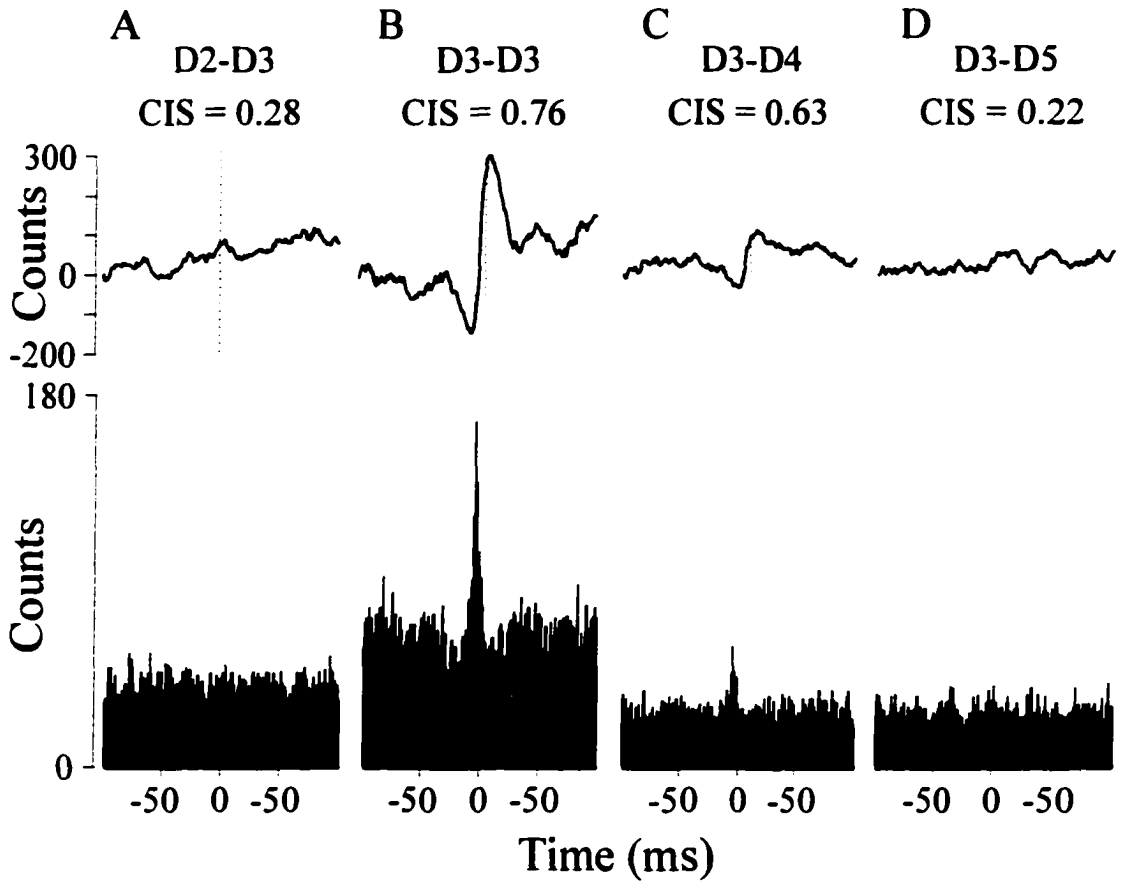

FIGURE 5.2 Example cross-correlation histograms for combinations of ED motor unit pairs residing in D2-D3, D3-D3, D3-D4, and D3-D5 compartments in panels A – D, respectively. The magnitude of the synchronous peak was calculated as the total number of counts in the peak above that expected due to chance divided by trial duration. This index, referred to as common input strength (CIS), indicates the rate of extra synchronous impulses (i.e., extra imp./s). The traces above each histogram are the cumulative sum (cusum) used to determine the location of the peak. The degree of synchrony was greatest for motor unit pairs within the same compartment (D3-D3) indicating that last-order inputs project differentially across the motor neurons supplying different compartments of ED.

D2/D3 (n = 12), 0.55 ± 0.26 (n = 18) for D3/D4, and 0.42 ± 0.15 for D4/D5 (n = 32). The CIS values for different extra-compartment motor unit pairs were significantly different from one another ($P<0.001$). The CIS values for pairs of motor units in the D2/D3 finger compartments were significantly smaller than for motor unit pairs in the D3/D4 or D4/D5 compartments. Only 3 pairs of motor units were recorded in non-adjacent compartments with each of these having one unit in the D3 compartment and the other unit in the D5 compartment of ED. The mean CIS for these 3 pairs of motor units was low at 0.14 ± 0.07.

The mean CIS value for all eighty intra-compartment motor unit pairs was 0.7 ± 0.3 (Figure 4). In comparison, the mean CIS value for the sixty-five extra-compartment motor unit pairs was 0.4 ± 0.22 which was significantly smaller ($P < 0.001$) than the CIS values for intra-compartment motor unit pairs.

DISCUSSION

The main finding of the present study was that the degree of synchrony for motor units within compartments of ED was markedly greater than across compartments. A modest degree of synchrony also existed for motor unit pairs in neighboring compartments. Therefore, last-order synaptic projections are not likely to be distributed uniformly across the entire pool of motor neurons innervating ED. Rather, last-order projections appear to supply predominantly sub-sets of motor neurons innervating specific finger compartments of ED. Consequently, motor neurons innervating specific compartments may be activated differentially to facilitate movements of individual fingers. Nevertheless, extra-compartmental synchrony suggests the existence of some

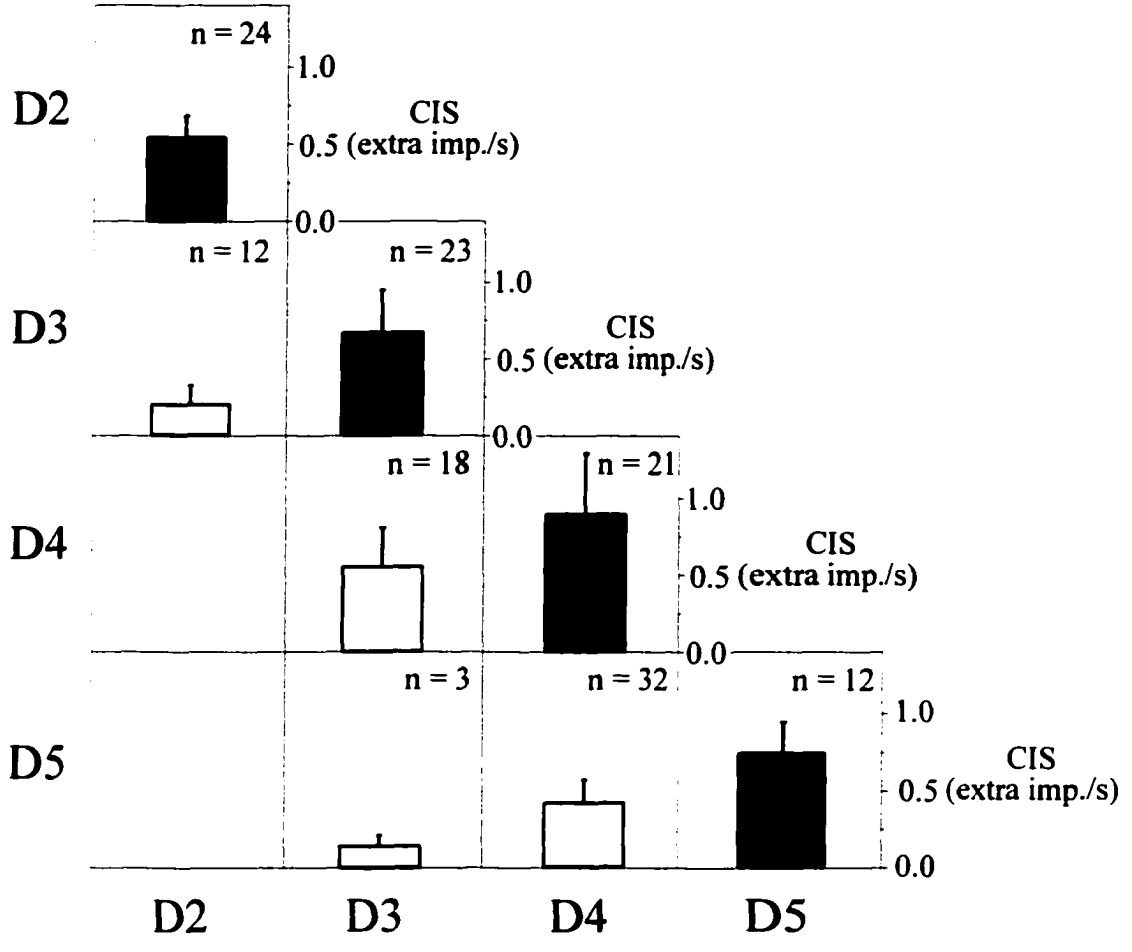

FIGURE 5.3 Matrix of mean (±SD) common input strength (CIS) within (filled bars) and across (open bars) compartments of ED. Each element of the matrix indicates the mean CIS value for motor unit pairs within the corresponding compartments indicated on the abscissa and ordinate. For motor units within the same compartment, the CIS values for D2/D2 were significantly less than for D4/D4. For extra-compartment motor unit pairs, the CIS values for D2/D3 were significantly less than for either D3/D4 or D4/D5. No statistical comparisons were made for the three pairs of D3/D5 motor units. The total number of motor unit pairs used for each comparison between and within compartments is given.

degree of across-compartment divergence that may contribute to inadvertent movement of neighboring fingers when attempting to move a single finger (Robinson and Fuglevand 1999; Häger-Ross and Schieber 2000).

Numerous other studies have examined the extent of motor unit synchrony in muscles that control the digits. In the majority of cases, motor units within a single muscle that control the fingers and hand exhibit significant synchrony (Bremner et al. 1991a; Datta and Stephens 1990; Milner-Brown et al. 1975). Direct quantitative comparison between those studies and the present one is difficult because different indexes have been used to calculate synchrony. Some studies, however, have used the same synchrony index as used in the present investigation. For example, Nordstrom et al. (1992) and Semmler and Nordstrom (1995) reported mean CIS values for pairs of motor units within the first dorsal interosseous, an intrinsic hand muscle, of 0.46 and 0.35, respectively. Consequently, the extent of motor unit synchrony for motor unit pairs within an intrinsic hand muscle may be less than for motor unit pairs within a single compartment of ED (mean CIS = 0.7, present study), an extrinsic hand muscle. Likewise, the mean CIS for motor unit pairs within flexor pollicus longus, an extrinsic hand muscle that acts to flex the thumb, was found to be 0.56 (Hockensmith and Fuglevand 2000). This is also slightly lower than for motor unit pairs residing in the same compartment of ED in the present study. These findings suggest that presynaptic fibers branch extensively across most of the neurons comprising a single motor nucleus in muscles that control the digits of the human hand (Sears and Stagg 1976).

The extent of synchrony for motor unit pairs in ED has been examined previously by

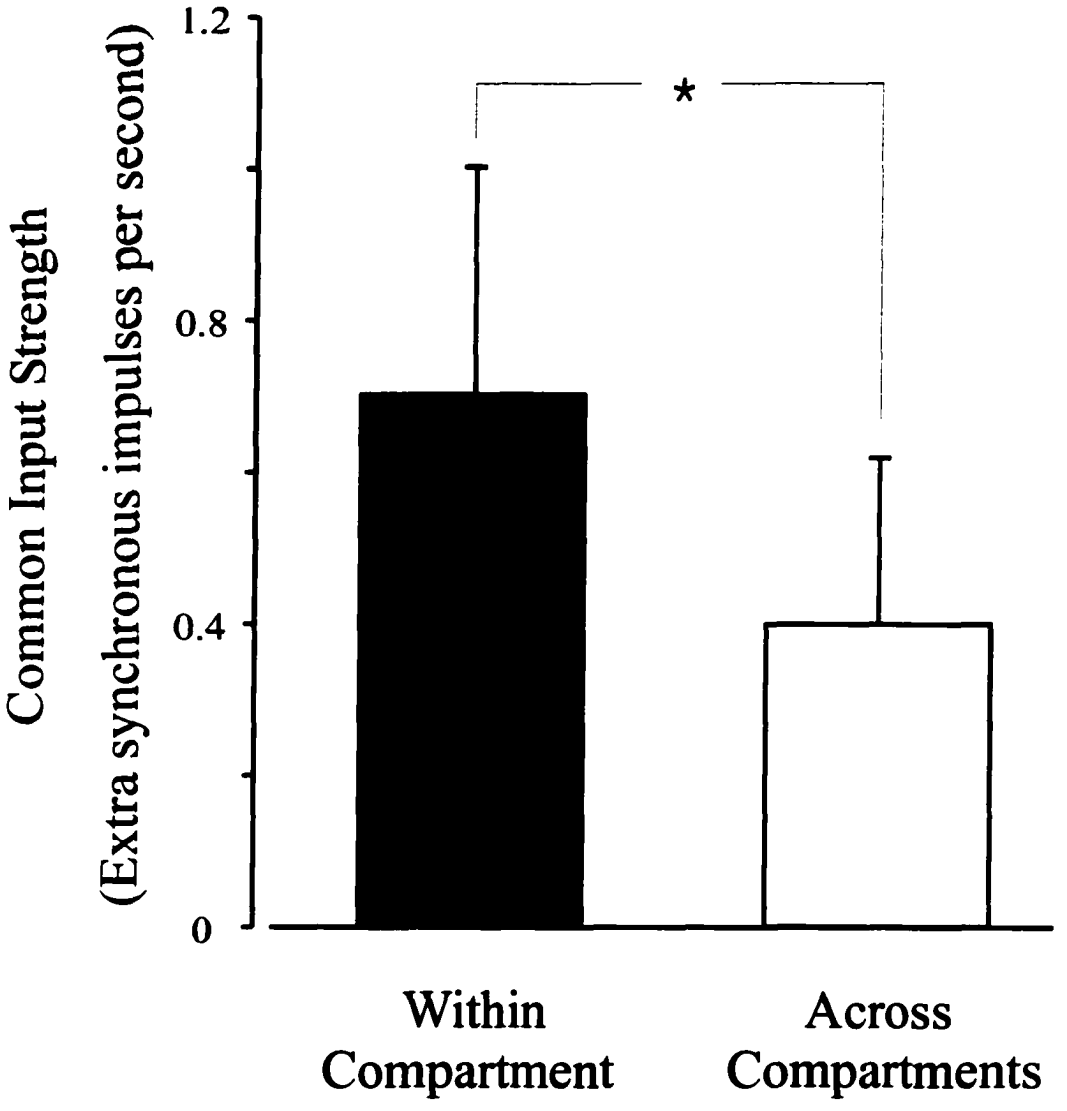

FIGURE 5.4 Mean (±SD) CIS for all intra-compartment motor unit pairs (filled bars) and extra-compartment pairs (open bars) of ED. The mean CIS value (0.7 ± 0.3) for the eighty motor unit pairs within a single compartment was significantly greater ($P<0.001$) than the mean CIS value (0.4 ± 0.22) for the sixty-five motor unit pairs that resided in different compartments. Therefore, last-order projections appear to predominantly supply subsets of motor neurons innervating specific finger compartments.

Schmied et al. (1993). They reported that significant cross-correlogram peaks occurred more frequently when both motor units were activated by extension of a single finger compared to motor units that were activated by extension of different fingers. This result is consistent with our finding of higher synchrony for intra versus extra-compartment pairs of motor units. The CIS values for motor unit pairs activated by extension of a single digit in the study by Schmied et al. (CIS = 0.44), however, were lower than those for motor units recorded in the same muscular compartment in the current study (CIS = 0.70). This discrepancy may partially be due to differences in the methods used to identify the compartment that each motor unit was located within. It is possible that some pairs of units designated by Schmied and colleagues to be activated by a single finger might have been characterized as extra-compartmental based on criteria used in the present study.

In addition to extensive distribution of synaptic input across motor neurons supplying an individual muscle, there is also strong anatomical (Shinoda et al. 1981) and physiological (Cheney and Fetz 1980; Lemon et al. 1986) evidence that cortico-spinal axons in non-human primates diverge to supply more than one motor nucleus. Consistent with these findings, the discharge times of motor units residing in different hand muscles of humans also exhibit synchrony, but usually to a lesser extent than motor units residing in the same muscle (Bremner et al. 1991a; Bremner et al. 1991b; Gibbs et al. 1995). In general, Bremner et al. (1991b) reported that the amount of synchrony for motor unit pairs residing in the same muscle was on average almost twice as great compared to motor unit pairs in different hand muscles. Interestingly, we found a qualitatively similar

ratio of about double the amount of synchrony for motor unit pairs within compartments (CIS = 0.7) versus across compartments (CIS = 0.4) in ED. This may indicate that the extent of shared last-order inputs onto motor neurons supplying different compartments of a single multi-tendoned hand muscle is similar to the extent of common last-order input onto different intrinsic hand muscles. Extensive distributed last-order inputs onto more than one motor nucleus involved in hand movements might even underlie the coordination of multiple muscles needed to perform specific movements. Indeed, Hockensmith and Fuglevand (2000) showed that the degree of synchrony for motor units in different muscles involved in the pinch grip was similar to the extent of synchrony for motor unit pairs residing within a single hand muscle. This suggests that the degree of common last-order synaptic inputs across motor neuron pools supplying two muscles that are habitually activated together was similar to that for motor neurons supplying an individual muscle. Thus, it seems probable that such divergence would exist across motor neurons supplying different compartments of a single multi-tendoned muscle like ED.

Indeed, a modest degree of synchrony was found for motor unit pairs that resided in different compartments of ED in the present study (CIS = 0.4) and by Schmied et al. (CIS = 0.36, 1993). In the present study, the degree of synchrony for pairs with one motor unit in the D4 compartment and the other motor unit in either of the neighboring compartments (D3 or D5) was significantly greater than for motor unit pairs in the D2/D3 compartments. This suggests that the last-order inputs onto motor neurons that predominantly supply the D4 compartment of ED may branch and terminate to a greater

extent on motor neurons innervating neighboring compartments compared to inputs that primarily target motor neurons supplying other compartments. Consequently, when attempting to activate motor neurons innervating the D4 compartment of ED, branches from of the last-order inputs may activate to some extent motor neurons innervating muscle fibers in the D3 and D5 compartments of ED. If unopposed by antagonistic muscle activity, this may result in the some extension of D3 and D5 when attempting to extend only D4. Indeed, studies that have measured the relative independence of finger movements in humans (Robinson and Fuglevand 1999; Häger-Ross and Schieber 2000) have found that fingers do not move independently of one another. These studies also reported that the least independent finger movement is extension of D4. Furthermore, both of these studies reported that extension of D2 was the most independent movement compared with extension of the other fingers. These behavioral findings roughly coincide with the general pattern of motor unit synchrony observed across compartments of ED in the present study.

Finally, the modest degree of synchrony across muscle compartments of ED may have also contributed to the broad distribution of spike-triggered average motor unit force in ED described in chapter 3. The technique of spike-triggered averaging was used to extract the contribution of ED motor units to each of the four fingers during a voluntary contraction. This technique involves the creation of an event channel representing the timing of discharges of accepted action potentials for a motor unit. The event channel is used as a trigger to send a brief time segment of each force channel to an averaging algorithm (Stein et al. 1972; Stephens and Usherwood, 1977). Consequently, the

resulting spike-triggered average of each force channel can provide an estimate of the force produced by the reference motor unit on each of the fingers. However, this method is strictly valid only when the other active units discharge independently of the target unit (Milner-Brown et al. 1973c). Motor units that exhibit some synchrony with the reference unit but reside in different compartments may augment the spike-triggered average force detected on the other fingers. Recently, it has been demonstrated that even a modest degree of synchrony results in large errors in the spike-triggered average force (Fuglevand 2001; Taylor et al. 2002). Consequently, the modest degree of synchrony found between motor units in neighboring compartments of ED may have resulted in an apparent broad distribution of motor unit force seen in the study described in chapter 3.

In summary, the degree of synchrony for motor unit pairs within a compartment of ED was significantly greater than for motor unit pairs in neighboring compartments indicating that the population of motor neurons innervating ED is coarsely segregated into four separate pools of motor neurons. Furthermore, based on our observations of the degree of synchrony across compartments, it appears that the last-order projections supplying motor neurons innervating one compartment of ED diverge to supply motor neurons innervating other compartments of ED. This was particularly true for inputs primarily directed to motor neurons innervating the D4 compartment of ED. This distributed input may result in an inability to selectively activate neurons innervating specific compartments and contribute to the extension of other fingers when attempting to move only one finger.

CHAPTER 6

INTRANEURAL MICROSTIMULATION INDICATES THAT MOTOR UNITS IN HUMAN EXTENSOR DIGITORUM EXERT FORCE ON INDIVIDUAL FINGERS

INTRODUCTION

Over the past thirty years, much of the information on motor unit contractile properties in humans has been derived using spike-triggered averaging. Spike-triggered averaging is a method whereby the average force transient associated with the discharge of a motor unit can be extracted from the whole muscle force signal. This method is strictly valid, however, only when other motor units discharge independently of the reference unit (Milner-Brown et al. 1973c).

In chapter 3, we used spike-triggered averaging to assess the distribution of force for extensor digitorum (ED) motor units across the fingers. Based on the observed profile of spike-triggered averages, we concluded that ED motor units distribute force broadly over the fingers. Subsequent to those findings, we found that motor units in different compartments of ED demonstrate a modest degree of synchrony (Chapter 5). Furthermore, it has recently been shown that even weak synchrony may result in large errors in spike-triggered average forces (Fuglevand 2001; Taylor et al. 2002). Consequently, the broad distribution of ED motor unit force observed using spike-triggered averaging may have been partly due to a modest degree of synchronous discharge of motor units in neighboring compartments. Therefore, the purpose of this study was to reevaluate the force distribution of motor units in ED using intraneural microstimulation of single motor axons, a method that is technically demanding but is not influenced by the activity of other units.

We found that intraneural microstimulation produced force almost exclusively on single digits. This suggests that most muscle fibers innervated by a motor axon are

confined to a single compartment of ED and that the weak synchrony between motor units in different compartments of ED may have led to the appearance of spike-triggered average force on multiple fingers.

METHODS

Twenty-six experiments were performed on 13 healthy human volunteers (6 female, 7 male, ages 20-42 years). The experimental procedures were approved by the Human Investigation Committee at the University of Arizona. The experimental set-up was similar to that described in the previous three chapters and therefore is briefly summarized here. Subjects were seated with their right elbow and wrist supported and immobilized with the forearm held in a semi-supinated position. The wrist was stabilized by padded vertical posts placed on either side of the distal forearm and the dorsal and palmer aspects of the hand. The fingers were flexed at a right angle at the metacarpophalangeal joints and maintained in this position by metal cuffs around the proximal interphalangeal joints that were attached to separate force transducers via light-weight cables (Figure 1A). The length of each cable was adjusted at the beginning of the experiment so that each digit was preloaded in this flexed position with a force of approximately 400 mN.

Force and EMG recording

Extension force of the digits was measured by four force transducers (Grass Instruments, Warwick, Rhode Island, model FT-10, range 0 – 1 N, sensitivity 156 mN/mV) mounted in a custom built manipulandum that allowed each transducer to be aligned with the proximal interphalangeal joint of the appropriate finger. The force

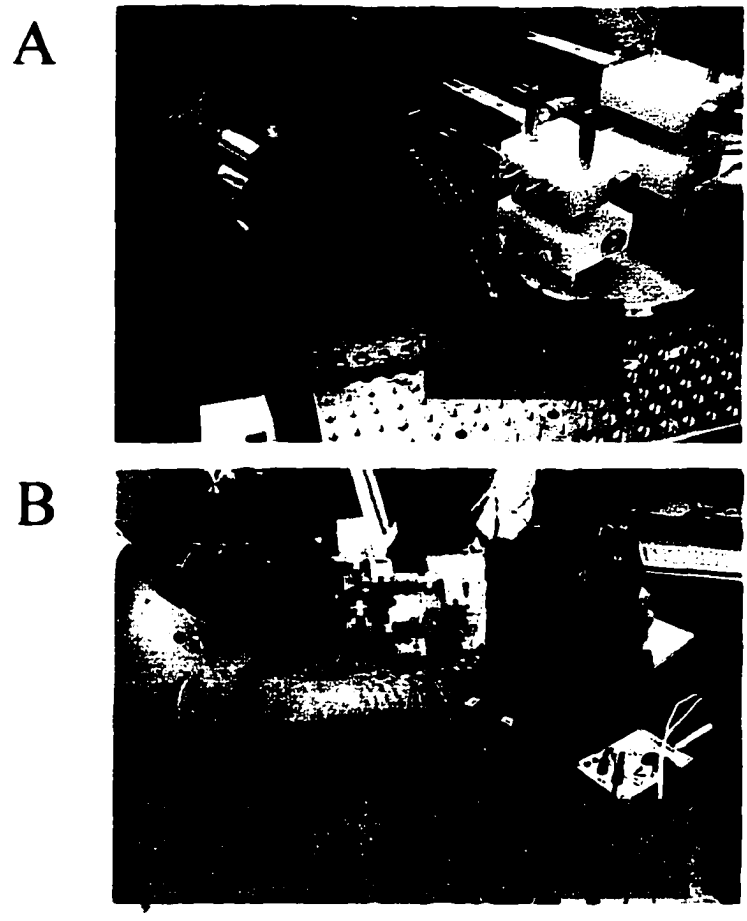

FIGURE 6.1 Front (A), and side (B) views of experimental set-up. A) Each finger was attached to a separate force transducer by a cable attached to a metal cuff surrounding the finger. The MCP joints of the fingers were maintained in a flexed position with a preload of ~ 400 mN to maintain ED in a lengthened position. B) A tungsten microelectrode was inserted into the lateral aspect of the upper arm approximately 10 cm above the lateral epicondyle of the humerus and gradually advanced until the microelectrode tip resided in the radial nerve. A surface electrode on the upper arm was used as a reference for the tungsten electrode. Four intramuscular electrodes were inserted into the four compartments of ED to record motor unit action potentials. Surface electrodes over the radius were used as references for the tungsten electrodes.

signals were amplified (X 1000) (World Precision Instruments, Sarasota, Florida) and displayed on oscilloscopes.

Electromyographic (EMG) responses to intraneural stimulation were recorded with sterilized tungsten microelectrodes (Frederick Haer & Co. Bowdoinham, Maine, 250-μm shaft diameter, ~ 4 kΩ impedance at 1000 Hz) with 2 to 3 mm of insulation removed from the tip, inserted into each of the four compartments of ED (Figure 1B). Placement of the EMG electrodes in the different compartments of ED was verified by electrical stimulation (100 to 300 μA, delivered at 1 pulse/s). Four surface electrodes (4 mm diameter Ag-AgCl) attached to the skin overlying the radius served as reference electrodes for the intramuscular EMG electrodes. The EMG signals were amplified (X 1000), band pass filtered (0.3-1 kHz) (Grass Instruments, Warwick, Rhode Island), and displayed on oscilloscopes.

Nerve Stimulation

A hand-held bipolar electrode with saline soaked pads (interelectrode distance of approximately 2 cm) was used to deliver stimuli percutaneously to estimate the path of the underlying radial nerve. Stimuli consisted of 4 – 8 mA constant current pulses delivered at 1 Hz (Grass Instruments, Warwick, Rhode Island, Stimulus Isolator, model SIU7). The electrode was initially located along the lateral aspect of the upper arm approximately 10 cm above the lateral epicondyle of the humerus and was moved in small steps proximally and distally to determine the optimal site that evoked the greatest extension force in the fingers for a given amount of current. This site was marked with

ink and used as a guide for the subsequent insertion of the tungsten microelectrode. The entire area was then cleansed with alcohol.

An insulated tungsten microelectrode (Frederick Haer & Co. Bowdoinham, Maine, 1- to 5-μm tip diameter, 250-μm shaft diameter, ~ 200 kΩ impedance post-insertion at 1000 Hz) was inserted through the skin in the upper arm at a site determined by percutaneous stimulation (Figure 1B). The electrode was slowly advanced three to five centimeters in an attempt to penetrate the radial nerve while negative current pulses (15-20 μA, 0.2 ms width, 1 Hz) were delivered through the electrode. A surface electrode (4 mm diameter Ag-AgCl) attached to the skin overlying the lateral aspect of the upper arm served as the reference electrode. This would be in contrast to our population of motor units recorded in chapter 3 using spike-triggered averaging, which was biased toward low-force motor units. Often multiple insertions of the electrode were required until weak stimulation evoked muscle twitches of ED. If twitches or parathesias could be elicited at stimulus currents $\leq$ 15 μA, then it was assumed that the electrode had penetrated the nerve. Minute adjustments of electrode position were then made in an attempt to find a site where a single motor axon innervating ED could be activated in isolation.

To determine if a single motor axon could be activated, stimulus intensity was first slowly increased until all-or-none responses occurred concurrently in the EMG and force signals. At a threshold level, stimuli may evoke all-or-none responses intermittently. Further increases in stimulus intensity above threshold resulted in consistent EMG and

force responses and ultimately a step increase in both of these signals. Stimulus intensity was then decreased to evoke single unit EMG and force responses.

Protocol

When an intraneural stimulation site yielded a unitary response, the single motor axon was stimulated at 1 Hz for approximately 1 minute. Subsequently, motor units were also stimulated at 20 Hz for a 2 second period. Stimulation at this higher frequency evoked a tetanic contraction allowing a better signal to noise ratio than individual twitches. Extension force of each finger, intramuscular EMG and the stimulus pulses were digitally sampled at approximately 2.5, 18.5 and 20 kHz, respectively, using the Spike2 data acquisition and analysis system (Cambridge Electronics Design, Cambridge, England).

Data Analysis

Data were analyzed off-line using Spike 2 and custom designed software. Twitch amplitude, contraction time, and half-relaxation time were analyzed from an ensemble average of 5 to 10 responses. Twitch amplitude was calculated from baseline to the peak force exerted on each finger. Total motor unit force was calculated as the sum of the peak force across all fingers. Unweighting of preloaded flexion force was treated as a negative force. Contraction time was measured from the initial rise in force to peak force. Mean contraction time was then calculated for the four fingers. Half-relaxation time was measured from the peak force until the force decayed to half of the twitch force for each finger. If a motor unit produced no force on a digit, the contraction and half-relaxation times for that digit were omitted.

Force produced by stimulation at 20 Hz was measured as the average force during the middle second of stimulation relative to a baseline force for each finger. Occasionally the baseline force drifted during the two seconds of stimulation. Therefore, to account for the changing baseline, force was measured immediately before and after the 2 seconds of stimulation. The baseline force was then taken as the slope between these two points and force at any point was calculated relative to this baseline. Total tetanic motor unit force at 20 Hz stimulation was calculated as the sum of the force for all fingers.

A selectivity index (Schieber et al. 1997) was used to quantify the distribution of force across the four fingers in response to electrical stimulation of single motor axons. Calculation of the selectivity index was described in chapter 3. Conceptually, a selectivity index of 1.0 represents a site where stimulation transmitted all of its force to one finger, whereas a selectivity index of 0.0 indicates a stimulation site in which evoked force was evenly distributed across the fingers. A preferred finger was designated for each motor unit based on the digit to which the stimulation produced the most force.

A one-way ANOVA was used to compare the selectivity index across fingers. A Student's t-test was used to compare selectivity index values obtained by intraneural microstimulation of single motor axons and spike-triggered averaging of single motor units. Values are reported as means ± standard deviation with a probability of 0.05 selected as the level of significance.

RESULTS

The current chapter reports the contractile properties and force distribution across the four fingers in response to intraneural microstimulation of single motor axons at 1 and 20 Hz for 18 motor units in human ED. Intraneural microstimulation at 20 Hz was successful in 12 of 14 units and was not attempted in the initial 4 motor units.

An example of threshold responses for stimulation of a single unit is shown in Figure 2A. The lower four traces are the force recordings for digits 2 through 5. Above the force traces are 11 stimuli delivered at 1 Hz. Directly above the stimuli are the intramuscular EMG traces for digits 2 through 5, respectively. In this example, a current of approximately 7 μA elicited an all-or-none response to 7 of the 11 stimuli (denoted by the arrows). The EMG and force responses associated with the delivery of the seven stimuli denoted by arrows in panel A are shown overlayed on an expanded time scale for digits 2 – 5 in panels B – E, respectively. The time scale for the EMG responses is briefer than for the force responses and the stimulus artifacts are denoted with asterisks. The baseline force detected at stimulus delivery has been subtracted from each force trace. The superimposed force traces for digit 2 demonstrate a consistent twitch transient which was coupled with an EMG signal detected only in the digit 2 compartment of ED. Only a small amount of force that was more variability for each twitch was recorded on digits 3 and 4. No detectable force was measured from D5.

Examples of the force records and superimposed EMG responses from four different ED units during 20 Hz stimulation are shown in Figure 3. Each of these four examples was obtained in a different experimental session. In each example, the lower four traces

show the force recordings for digits 2 through 5. Above the force traces are the stimuli delivered at 20 Hz for two seconds. Directly above the stimuli are the 40 intramuscular EMG responses overlayed on an expanded time scale for digits 2 through 5, respectively. For the unit depicted in panel A, approximately 20 mN of force was produced on digit 2 with little force developed on the other digits resulting in a selectivity index of 0.92. An intramuscular EMG response was detected only in the D2 compartment of ED. In panel B, a unit produced force fairly selectively on digit 3 with a little force also evident on digit 4 resulting in a selectivity index of 0.86. Stimulation of this motor unit resulted in an intramuscular EMG response isolated to the D3 compartment of ED. Panel C depicts a unit that produced approximately 60 mN of force on digit 4 and a small amount on digit 3. This unit had a selectivity index of 0.91 and displayed a consistent EMG response in the D4 compartment of ED. Lastly, the motor unit shown in Panel D produced force very selectively on D5 with an unloading of D4 and D3 and consequently had a selectivity index of 1.12. The only detected intramuscular EMG signal time-locked to the stimulus was in the D5 compartment of ED. Therefore, force produced by intraneural microstimulation of different motor units was focussed on individual digits with EMG responses recorded in the associated compartment of ED.

Contractile Properties

The mean contraction time for the 18 motor units recorded in the present study was 50.7 ± 11.5 ms (range: 26.3 - 76 ms), which is similar to that reported for motor units in other hand muscles obtained with intraneural microstimulation (50 ms, Thomas et al. 1990a; 57 ms, Fuglevand et al. 1999). Interestingly, Macefield et al. (1996) reported a

FIGURE 6.2 Example force and EMG recording of ED during 1 Hz stimulation of a single motor axon in the radial nerve at threshold (A). Arrows denote an evoked response in both the EMG and force records. This unit produced all-or-none responses concurrently in both the EMG and force records in the D2 compartment of ED and on D2, respectively. Superimposed EMG and force responses for digits 2 through 5 for the 7 stimuli indicated by arrows in A are shown in panels B through E, respectively. It is evident from the superimposed EMG responses that motor unit activity was only detected in the D2 compartment of ED. Asterisk below each superimposed EMG trace indicates stimulus artifact. Superimposed force traces show consistent twitch responses of D2.

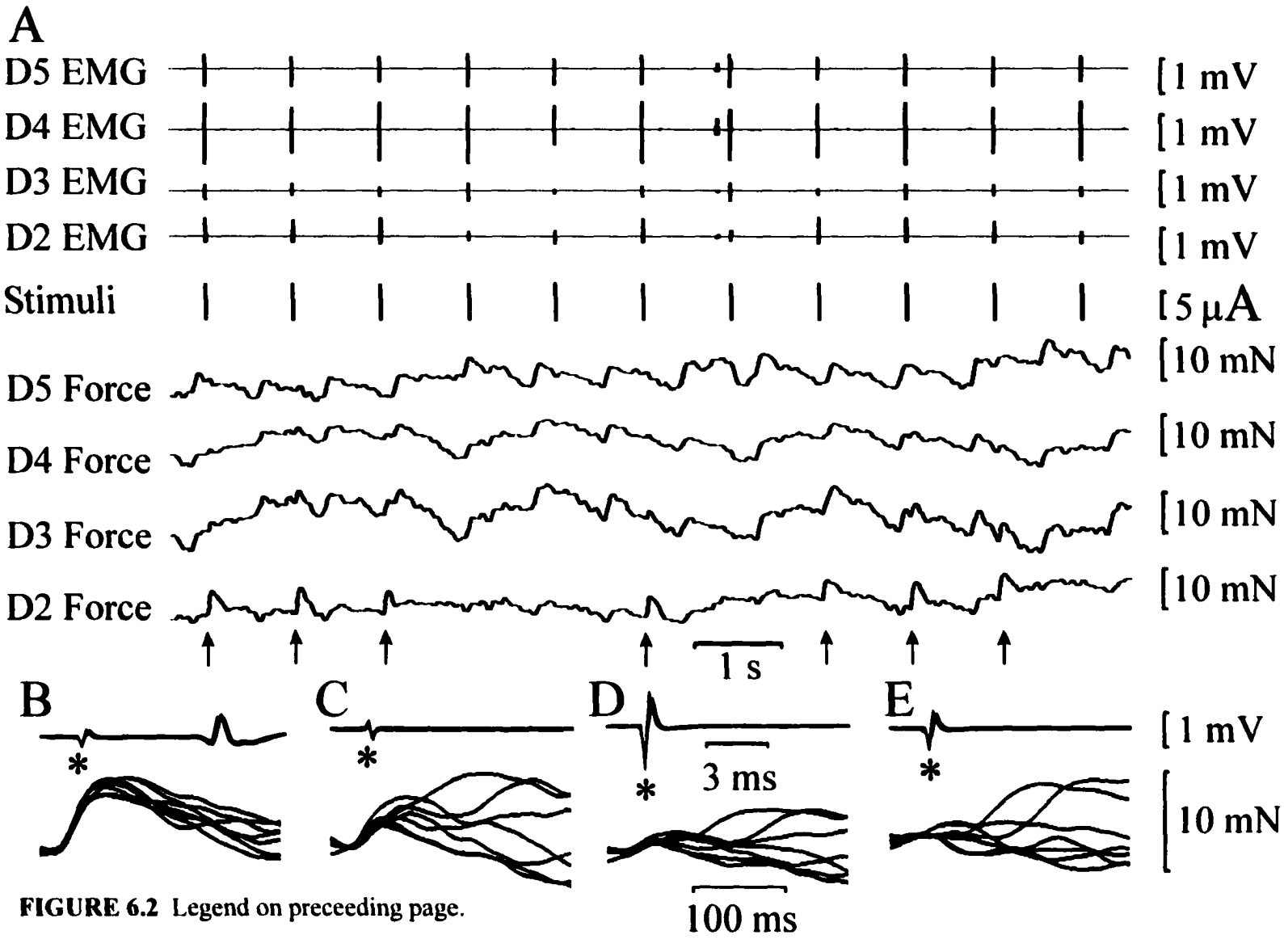

FIGURE 6.2 Legend on preceeding page.

longer mean contraction time of 75 ms in toe extensor motor units. The mean contraction time for ED motor units reported in the present study utilizing intraneural microstimulation was slightly longer than that obtained using spike-triggered averaging (43 ms) as described in chapter 3 of this dissertation. Mean half relaxation time was 56.6 ± 10.9 ms (range: 40.5 - 74 ms) which is comparable to that reported by Thomas et al. (1990a) for thenar motor units (59 ms) but briefer than that reported for intrinsic finger muscles and extrinsic finger flexors (71 ms, Fuglevand et al. 1999) and toe extensors (78 ms, Macefield et al. 1996).

For the 18 motor units in the present study, when stimulated at 1 Hz, the average twitch force was 13.8 ± 10.3 mN (range: 2.7 - 37.7 mN). This value is very similar to the twitch force of ED motor units assessed by spike-triggered averaging discussed in chapter 3 and thenar motor units utilizing intraneural microstimulation (11 mN, Thomas et al. 1990a). That the force values assessed by either spike-triggered averaging or by intraneural microstimulation were similar was somewhat surprising. It is known that the technique of spike-triggered averaging preferentially samples low-threshold and consequently low force motor units. Alternatively, with intraneural microstimulation, if two motor axons were equidistant from the current source, the larger axon would be preferentially recruited (Mortimer 1981). Consequently, this may have biased our sample of motor units obtained with this technique towards larger motor units. However, because the majority of motor units innervating a muscle are low-threshold units with smaller motor axons (Enoka and Fuglevand 2001), it is likely that the current source during intraneural microstimulation was in close proximity to one of these smaller motor

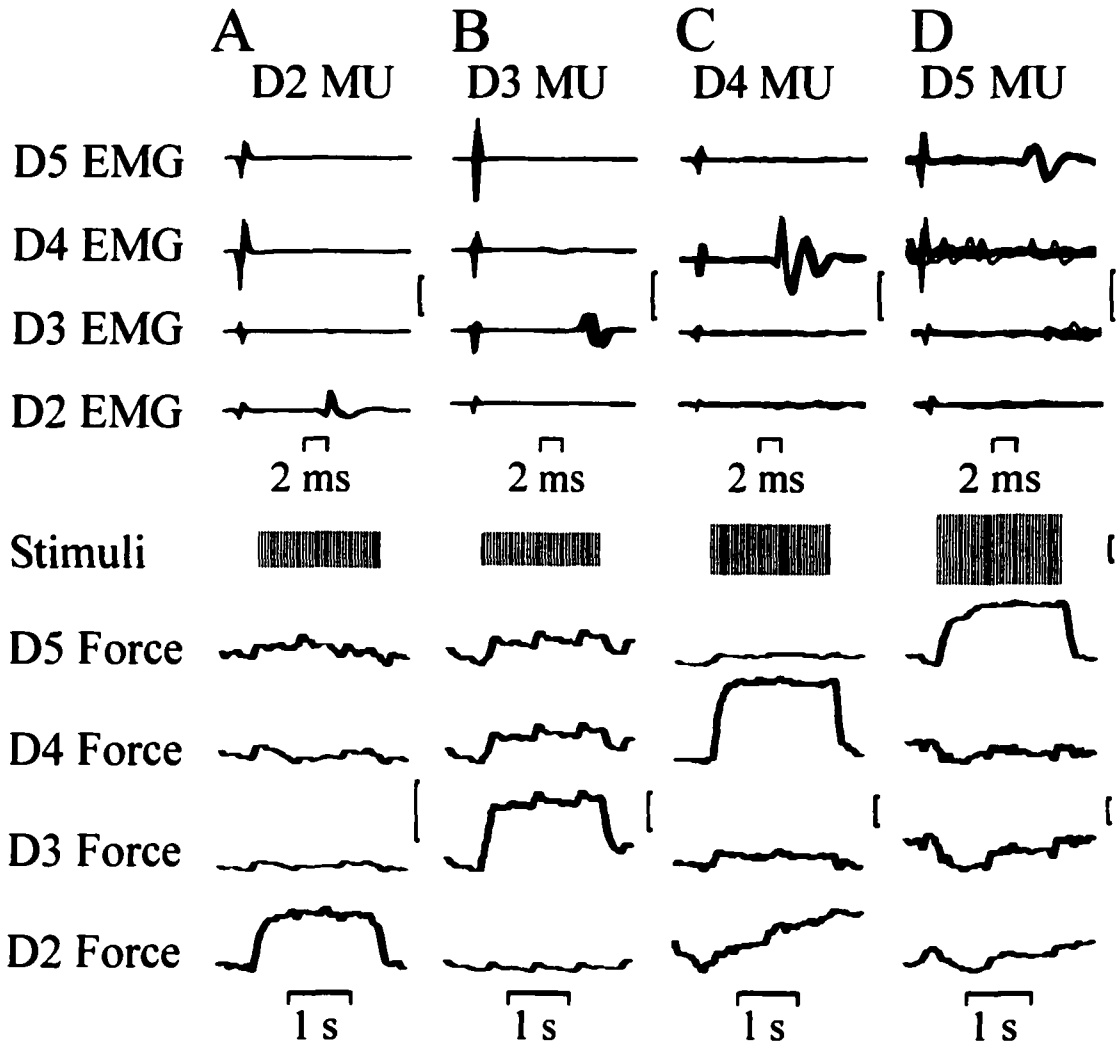

FIGURE 6.3 Force records and superimposed EMG responses from four different motor units (A-D) innervating ED during 20 Hz intraneural microstimulation. These motor units evoked extension force selectively on D2 through D5 with SI values of 0.92, 0.86, 0.91, and 1.12, A – D respectively. Coupled with the force for each unit is an EMG response in the expected compartment of ED. Calibration bars of the EMG are 1 mV for the D2 and D4 motor units and 0.5 mV for the D3 and D5 motor units. Calibration bars for the force records are all 20 mN. Calibration bar for the stimulus pulse is 5 μA.

axons. Other investigators who have also used intraneural microstimulation reported larger twitch amplitudes of 20 mN for toe extensor muscles (Macefield et al. 1996) and approximately 55mN for intrinsic finger muscles and extrinsic finger flexors (Fuglevand et al. 1999). There was no correlation between motor unit twitch force and either contraction or half-relaxation times, which may partly be due to the small sample size of the present study. Twelve of the motor units were also stimulated at 20 Hz and the average total force was 34.9 ± 26.5 mN (range: 9.9 to 102.5 mN).

Force Distribution

The mean selectivity index for the 18 motor units based on twitch forces was 0.73 ± 0.32 with a range 0.21 to 1.49. Examples of spike and stimulus-triggered average forces on each finger in response to voluntary activation and intraneural stimulation at 1 Hz is shown in Figure 4. Panel 4A is an example of the force distribution of a single motor unit assessed by spike-triggered averaging and was obtained in an earlier set of experiments. This particular motor unit produced the most force on digit 4, a comparable amount of force on digit 3 and some force on digits 2 and 5. Therefore, the force from this particular motor unit was broadly distributed across the fingers, indicated by a relatively low selectivity index of 0.34. The forces in Figure 4B were obtained in the present study by stimulus-triggered averaging of the force records based on the delivery of intraneural stimuli. In this example, most of the extension force was produced on digit 3 with only a little force developed on digits 2 and 4. Therefore, the force was directed primarily to a single digit and consequently the selectivity index for this motor unit was

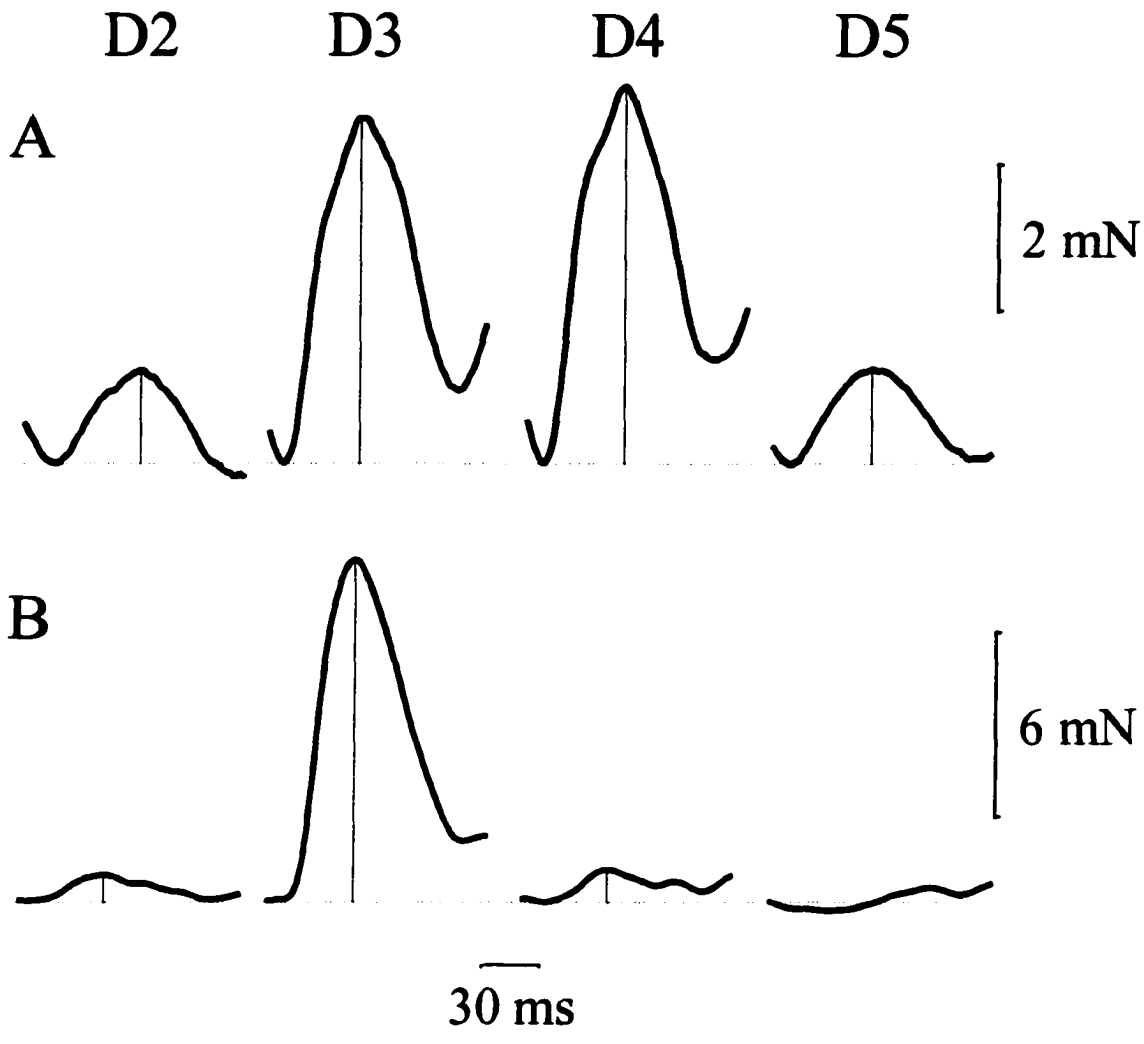

FIGURE 6.4 A comparison of (A) spike and (B) stimulus-triggered average forces on each finger in response to voluntary activation and intraneural microstimulation of a single motor axon innervating ED, respectively. Both techniques give an estimate of the force produced by a single motor unit on each digit. A) However, the spike-triggered average force records may be distorted by the synchronous discharge of other active motor units. B) Intraneural microstimulation is a method that is not influenced by the activity of other units and produces force significantly more selectively on individual fingers.

0.9. The high selectivity index was a feature of most of the units studied using microstimulation in the present study.

The distribution of motor unit force was also examined using intraneural microstimulation at 20 Hz which yielded a mean selectivity index of 0.92 ± 0.21 (range: 0.64 to 1.35). The mean selectivity index values of motor unit force were slightly higher in response to 20 Hz stimulation and were less variable than twitch forces evoked by single stimuli. Consequently, analysis of selectivity index was based on response to 20 Hz stimulation if available for a motor unit. A histogram comparing the force distribution of ED motor units assessed by intraneural stimulation and spike-triggered averaging according to the selectivity index is shown in Figure 5. The mean selectivity of 18 motor units (12 at 20 Hz) assessed by intraneural stimulation was 0.9 ± 0.28. In comparison, the selectivity index for 233 motor units obtained by spike-triggered averaging (chapter 3) was significantly smaller with a mean value of 0.38 ± 0.14 ($P <$ 0.01). Therefore, although both methods quantify the distribution of ED motor unit force across the fingers, motor unit force is significantly more focused to individual fingers when assessed with intraneural microstimulation. It is possible that the broadly distributed motor unit force measured by spike-triggered averaging may be the result of a modest degree of synchrony for motor units in different compartments of ED (Chapter 5).

Motor units were categorized according to the digit upon which they produced the greatest force, referred to as the preferred finger. Using this classification scheme, 6 motor units were designated to have digit 2 as the preferred finger, 6 units had digit 3 as the preferred finger, only 1 had digit 4 as the preferred finger, and 5 units had digit 5 as

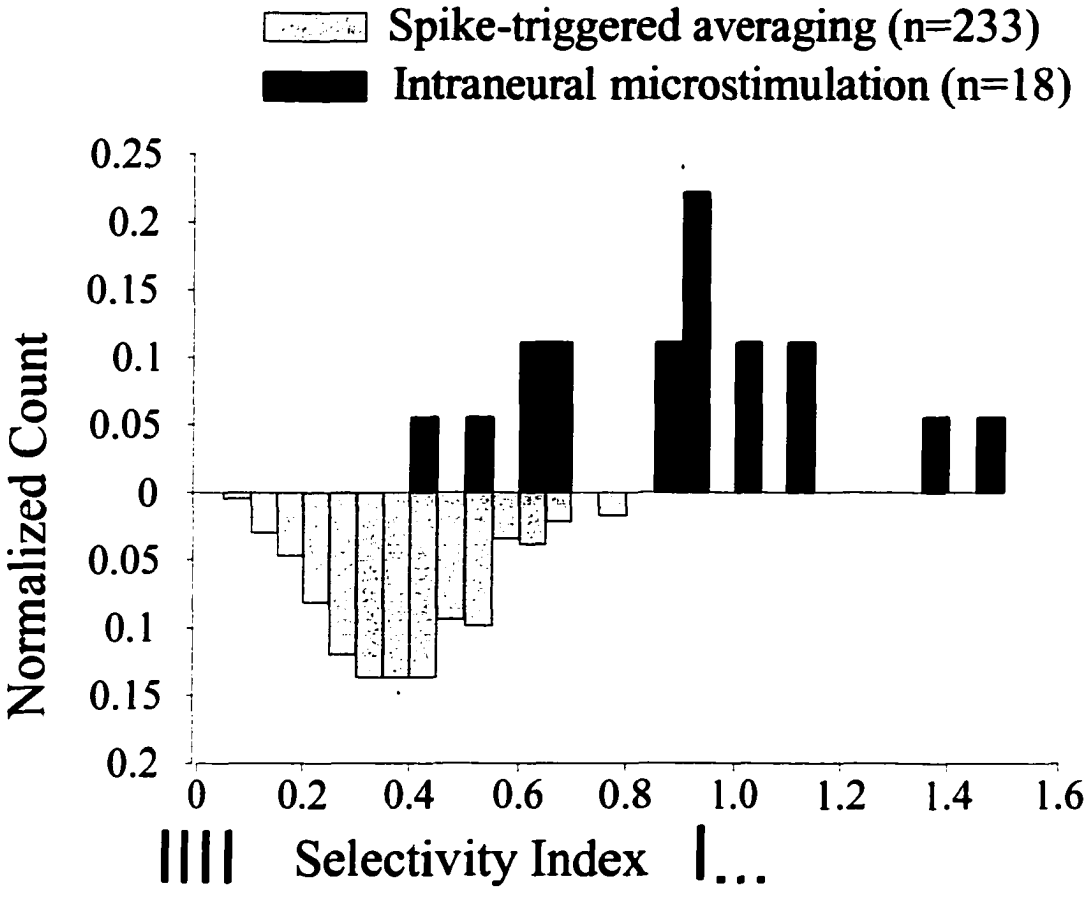

FIGURE 6.5 A comparison of the force distribution of ED motor units evoked by intraneural microstimulation or obtained by spike-triggered averaging according to the selectivity index. Force in 233 ED motor units appears to be broadly distributed across the fingers with a mean selectivity index of 0.38 ± 0.14 (arrow). However, intraneural microstimulation of 18 motor units in ED showed that motor unit force is selectively focused to individual digits with a higher mean selectivity index of 0.90 ± 0.28 (arrow). The selectivity index at 20 Hz stimulation was used in the 12 motor units in which it was successful. The icons below the selectivity icons of 0.0 and 1.0 symbolize an even distribution of force and force focused entirely on one digit, respectively.

the preferred finger. There was no statistical difference in the selectivity index across motor unit groups based on preferred finger. The mean selectivity index of motor units for preferred fingers of digits 2 through 5 was 0.85 ± 0.29, 0.83 ± 0.26, 0.91, and 1.04 ± 0.33, respectively. Because no difference in the selectivity index was found, the data were combined across fingers. The grouped data showed no significant correlation between motor unit force and selectivity. This differed from the finding in Chapter 3 of a weak correlation between motor unit force and selectivity with stronger motor units tending to have lower selectivity indices. The absence of a significant correlation in the present study may be partly due to the relatively small sample size.

DISCUSSION

The main finding of the present study was that force arising from intraneural microstimulation of single motor axons innervating ED is selectively focused on individual digits. This finding supports the conclusion of Chapter 4 that the junctuae tendinum plays only a minor role in the distribution of force across the fingers. Furthermore, it demonstrates that each finger is acted upon by ED through a discreet population of motor units. Consequently, ED can be characterized as a muscle comprised of four distinct compartments.

The neuromuscular apparatus may be segregated into different compartments for at least three reasons. First, the muscle mass itself may be separated morphologically into discernable compartments by sheathes of connective tissue, muscle fiber architecture or by possessing multiple origins or insertions (Figure 6A). For example, the biceps femoris muscle of the cat is separated into 3 or 4 distinct compartments by connective tissue

sheathes (English and Weeks 1987; Chanaud and Macpherson 1991). In humans, the first dorsal interosseous muscle has two distinct heads or compartments, which arise from the first and second metacarpal bones (Platzer 1992). In addition, many of the primary finger flexors and extensors such as ED give rise to multiple tendons that insert into different fingers.

Second, a muscle may also be compartmentalized due to the spatial pattern of innervation (Figure 6B). For example it has been shown in several lower hindlimb muscles of many different species including the rabbit, rat, mouse, and turtle that type S motor units innervate type I muscle fibers predominantly in the central portion of a muscle. Conversely, type FR and FF motor units innervate type II muscle fibers in more superficial muscle regions (Laidlaw et al. 1995; Wang and Kernell 2001a; Wang and Kernell 2001b). Because type S motor units have lower threshold for recruitment (Burke 1981), the central region of the muscle may be preferentially activated for low force tasks such as walking. For tasks such as running or jumping that require more force, fast twitch fibers on the superficial aspect of the muscle are also recruited. Therefore, many of these hindlimb muscles may be compartmentalized due to the topographical distribution of different motor unit types.

Similarly, muscles may be compartmentalized due to spatial patterns of innervation because muscle nerves often ramify and give rise to several primary nerve branches that enter a muscle. For example, four primary nerve branches supply the cat lateral gastrocnemius muscle with each branch thought to innervate a different region of the muscle (English and Weeks 1984). Likewise, the radial nerve branches approximately

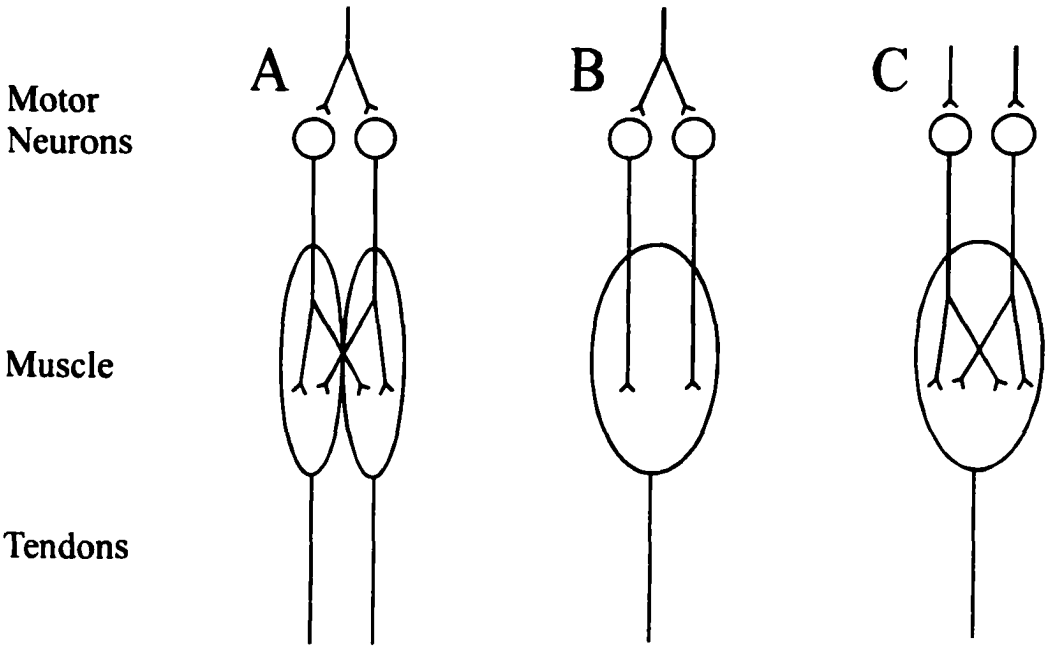

FIGURE 6.6 Schematic diagram depicting three different ways in which muscles may be compartmentalized. Ellipses represent different muscles or compartments of a muscle. A) Last-order projections uniformly supply motor neurons that innervate muscle fibers distributed throughout the muscle. However, the muscle itself is divided into compartments because of multiple tendons that emanate from the muscle. B) Last order inputs are evenly distributed across a motor neuron pool innervating a single muscle but motor neuron subpopulations innervate distinct regions of a muscle. C) Last-order inputs onto motor neurons that innervate a single muscle are segregated allowing selective activation of subpopulations of motor neurons.

four times upon entering ED (Abrams et al. 1997), consistent with the possibility that each primary nerve branch innervates a specific compartment of ED. However, it is also possible that, upon entering ED, each primary nerve branch innervates muscle fibers distributed throughout ED.

And third, compartmentalization can occur because the inputs onto the motor neurons innervating a single muscle are segregated (Figure 6C). For example, some motor units in the long head of the biceps brachii in humans are selectively active during supination of the forearm. In contrast, other motor units in the muscle are selectively active during elbow flexion (ter Har Romney et al. 1984). These findings suggest that the inputs onto the motor neurons innervating the long head of the biceps brachii are segregated and project to subpopulations of neurons controlling specific movements. Similarly, it has been demonstrated in hindlimb muscles of the cat that sensory projections back to homonymous motor neurons are not uniformly distributed. Rather sensory feedback seems to be stronger to motor neurons innervating the same muscle region that the afferent receptor resides in, which provides the means for a "sensory partitioning" of muscle (Botterman et al. 1981; Hamm et al. 1985; Vanden Noven et al. 1986; Windhorst et al. 1989).

Based on the results of the present study and previous experiments described in this dissertation, we believe that ED exhibits features of all three aspects of neuromuscular compartmentalization depicted in Figure 6. First, ED is a muscle that gives rise to four tendons that insert into each of the fingers. Consequently, although ED is not readily separated into discernable compartments by sheathes of connective tissue, it is speculated

that different regions of the muscle contribute force preferentially to specific tendons. Indeed we found that force arising from intramuscular stimulation of contiguous bundles of muscle fibers in different regions of ED was not evenly distributed across the tendons but focussed on individual fingers (Chapter 4). This suggests that four distinct compartments or muscle regions comprise ED which produce force relatively selectively on individual fingers.

Second, single motor units may have muscle fibers that are distributed throughout multiple compartments of ED, which would explain the broad distribution of spike-triggered average motor unit force reported in Chapter 3. However, the results of the present study demonstrate that force arising from stimulation of single motor axons is focussed on individual fingers. Consequently, muscle fibers belonging to a single motor unit are most likely confined to specific muscle regions that produce force relatively selectively on individual fingers.

Finally, we have shown in Chapter 5 that last-order synaptic projections are not likely to be distributed uniformly across the entire pool of motor neurons innervating ED. Rather, last-order projections appear to supply predominantly sub-sets of motor neurons innervating specific finger compartments of ED with a lesser extent of across-compartment divergence of last-order inputs. This conclusion was reached by estimating the extent of divergence in last-order inputs to motor neurons based on the degree of short-term synchrony among motor units within and across compartments of ED.

In summary, force arising from intraneural microstimulation of single motor axons innervating ED was highly focused on individual digits. Therefore, motor units most

likely innervate muscle fibers restricted to specific compartments of ED which are capable of producing force on individual fingers. Consequently, extension of an individual finger would require the selective activation of motor neurons innervating a specific compartment. However, it has been shown that humans do not move their fingers independently of one another (Robinson and Fuglevand 1999; Häger-Ross and Schieber 2000). Consequently, the lack of individuation in finger movements may be due to an inability to selectively activate a group of motor neurons innervating a single compartment of ED. This inability is most likely due to branched last-order inputs supplying motor neurons innervating different compartments of ED.

CHAPTER 7

SUMMARY AND CONCLUSIONS

The human hand has incredible dexterity and can perform a wide variety of coordinated movements such as manipulating a key into a door lock or playing a musical instrument. Lesions of the motor cortex due to stroke (Twitchell 1951) or damage to the corticospinal pathway (Lawrence and Kuypers 1968a) lead to prolonged loss of dexterity of the fingers. Consequently, there has been a substantial effort to understand the role that the motor cortex and corticospinal tracts play in controlling hand movements. However, to fully realize how the descending command ultimately produces finger movements, it is necessary to understand how muscles that control the fingers are organized.

Many of the muscles responsible for moving the fingers possess a single belly that gives rise distally to multiple tendons that insert onto all the fingers. It has been proposed that these multi-tendoned muscles consist of separate functional compartments that control individual fingers (Fritz et al. 1992). Accordingly, each compartment should be innervated by a discreet population of motor neurons that produce force onto one of the tendons. This organizational scheme should allow each finger to be controlled independently but is contingent on the force contributed by single motor units to act on individual fingers. Therefore, the initial objective of this dissertation was to examine the distribution of force from single motor units in a multi-tendoned muscle of the human hand, the extensor digitorum (ED), using the technique of spike-triggered averaging. Surprisingly, motor unit force was found to be broadly distributed across the digits and did not appear to be dedicated to individual digits. This finding raised several

fundamental questions about the musculotendonous and neural factors that might contribute to the broad distribution of motor unit force across the fingers.

Three specific factors that may play a role in the apparent coupling of force across the fingers were investigated. First, previous anatomical studies of the hand have revealed lateral connections between the distal tendons emanating from ED. Consequently, we hypothesized that linkages between the distal tendons of ED may cause force developed in a single compartment to be transmitted to neighboring tendons. This hypothesis was tested by intramuscular stimulation of small contiguous sets of muscle fibers in ED while recording the force response of the four fingers. Force arising from intramuscular stimulation was more focused to a single digit compared with spike-triggered average motor unit force. This result suggested that inter-tendonous connections account for only a modest amount of the broad distribution of spike-triggered average motor unit force observed in ED.

An alternative possibility was that our spike-triggered averages of motor unit force were contaminated by correlated activity among motor units residing in different compartments. A key assumption underlying the use of spike-triggered averaging is that the reference unit discharges independently of other concurrently active units. If motor units in different compartments were synchronously active to some degree with the reference unit, the spike-triggered average force would be comprised of the force of the reference unit and that contributed by coincidentally active units. Therefore, the degree of motor unit synchrony was measured both within and across the four compartments of ED. Strong motor unit synchrony was found for motor unit pairs within compartments. A

modest degree of synchrony for motor unit pairs in neighboring compartments was found that may have contributed to the broad distribution of spike-triggered average motor unit force. Furthermore, these results suggest that last-order synaptic projections may not be distributed uniformly across the entire pool of motor neurons innervating ED. Rather, last-order projections appear to predominantly supply sub-sets of motor neurons innervating specific finger compartments of ED but also branch to supply motor neurons innervating other compartments.

Another possible explanation for the broad distribution of motor unit force is that single motor axons may branch to innervate muscle fibers situated in multiple compartments of ED. This possibility was examined by measuring the force produced on each finger in response to intraneural microstimulation of single motor axons innervating ED. When assessed in this way, the force of ED motor units was found to be highly selective for a single digit. Therefore, it appears that the muscle fibers innervated by a motor axon are primarily confined to one of four compartments of ED.

In conclusion, the experiments described in this dissertation provide us insight into the neuromuscular organization of ED in particular and multi-tendon muscles in general. We found that both intramuscular stimulation of contiguous bundles of muscle fibers in ED and intraneural microstimulation of single motor axons innervating ED produced force fairly selectively on individual fingers. Consequently, it appears that ED may contain four muscular compartments and that muscle fibers innervated by ED motor units may be primarily confined within one of these compartments. However, while ED acts upon each finger through a discreet population of motor units, it may be difficult to

selectively activate a specific group of motor units which exert force on only one of the four tendons. This conclusion is based on the finding of a modest degree of short-term synchrony for motor unit pairs in neighboring compartments. Such short-term synchronization has been attributed in part to last-order divergent projections that provide common synaptic input across motor neurons (Sears and Stagg 1976; Kirkwood and Sears 1978; Nordstorm et al. 1992). Therefore, last-order synaptic projections, while predominantly supplying sub-sets of motor neurons innervating specific finger compartments of ED, also branch to supply motor neurons innervating other compartments. Consequently, when attempting to activate selectively a specific compartment of ED, divergence of last-order inputs across sub-sets of motor neurons may contribute to inadvertent activation of motor neurons innervating neighboring compartments. Ultimately, this may cause some movement of neighboring fingers when attempting to move a single finger, consistent with the findings of behavioral studies of finger movements (Robinson and Fuglevand 1999; Häger-Ross and Schieber 2000). Interestingly, studies that have measured the activity of many muscles in the forearm and hand when attempting to move a single finger have found several muscles to be active simultaneously (Rose et al. 1999). Therefore, when attempting to move a single finger, unwanted movements in neighboring fingers may be minimized by activation of multiple muscles. It is likely that this orchestration of coordinated muscle activity is mediated by descending commands originating from supraspinal motor areas that project to spinal interneurons and motor neurons.

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