Common Input to Motor Neurons Innervating the Same and Different Compartments of the Human Extensor Digitorum Muscle

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Keen, Douglas A. and Andrew J. Fuglevand. Common input to motor neurons innervating the same and different compartments of the human extensor digitorum muscle. J Neurophysiol 91: 57–62, 2004. First published September 10, 2003; 10.1152/jn.00650.2003. Short-term synchronization of active motor units has been attributed in part to last-order divergent projections that provide common synaptic input across motor neurons. The extent of synchrony thus allows insight as to how the inputs to motor neurons are distributed. Our particular interest relates to the organization of extrinsic finger muscles that give rise distally to multiple tendons, which insert onto all the fingers. For example, extensor digitorum (ED) is a multi-compartment muscle that extends digits 2–5. Given the unique architecture of ED, it is unclear if synaptic inputs are broadly distributed across the entire pool of motor neurons innervating ED or segregated to supply subsets of motor neurons innervating different compartments. Therefore the purpose of this study was to evaluate the degree of motor-unit synchrony both within and across compartments of ED. One hundred and forty-five different motor-unit pairs were recorded in the human ED of nine subjects during weak voluntary contractions. Cross-correlation histograms were generated for all of the motor-unit pairs and the degree of synchronization between two units was assessed using the index of common input strength (CIS). The degree of synchrony for motor-unit pairs within the same compartment (CIS = 0.7 ± 0.3; mean ± SD) was significantly greater than for motor-unit pairs in different compartments (CIS = 0.4 ± 0.22). Consequently, last-order synaptic projections are not distributed uniformly across the entire pool of motor neurons innervating ED but are segregated to supply subsets of motor neurons innervating different compartments.

INTRODUCTION

A fundamental issue that underlies the coordination of activity among a population of neurons relates to how synaptic input is distributed across the ensemble. In a landmark study, Mendell and Henneman (1971) used intracellular recordings to determine the proportion of motor neurons within a spinal motor nucleus that received synaptic input from single Ia afferent fibers. The remarkable finding of that investigation was that individual afferent fibers made synaptic contact with most, and in many cases all, homonymous motor neurons as well as with large numbers of motor neurons supplying synergistic muscles. Subsequent anatomical studies confirmed the existence of extensive ramification of individual Ia afferents throughout longitudinally oriented motor nuclei in the spinal cord (Brown and Fyffe 1978).

Much less is known about the distribution of individual descending and spinal interneuronal inputs to motor neurons. Some anatomical evidence indicates that terminal arbors of individual collaterals from corticomotoneuronal cells are distributed in longitudinal cylinders coterminal with motor nuclei in lamina IX of the spinal cord (Lawrence et al. 1985). Such findings are consistent with the possibility that these specialized descending inputs may contact a large proportion of neurons in a motor nucleus (Porter and Lemon 1993). Neurophysiological studies, although indirect, have demonstrated relatively extensive divergence of corticospinal inputs both within (Mantel and Lemon 1987) and across spinal motor nuclei (Asunuma et al. 1979; Buys et al. 1986; Fetz and Cheney 1980). Although little is known about the projection frequency of spinal interneurons, one estimate suggests that collaterals from individual Ia inhibitory interneurons may terminate in multiple motor nuclei and contact ≤20% of the motor neurons within these nuclei (Jankowska 1992). These observations suggest that synaptic inputs, with some exceptions, are broadly distributed across a motor neuron population (Binder et al. 1996). Therefore an important determinant of recruitment susceptibility and motor-unit activity appears to be related to the 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 that control a single muscle derives in part from these experimental observations on synaptic input organization.

It is unclear, however, how the inputs to a pool of motor neurons might be organized for a muscle that is subdivided into different compartments (Loeb 1990). One possibility is that the entire array of motor neurons that innervate a multi-compartment muscle may receive more or less similar inputs. Control over different parts of the muscle, therefore, could be affected by differences in intrinsic properties of motor neurons that innervate different parts of a muscle, such as occurs for deep and superficial regions of some hind limb muscles in rodents (Kernell 1998). Alternatively, motor neurons supplying different parts of a muscle might receive relatively distinct synaptic inputs (Bottomer et al. 1983; Hamm et al. 1986; Vanden Noven et al. 1986). In this case, activation of different parts of a muscle (or subsets of motor units) would depend primarily on the specific input pathways engaged. Consequently, it was of interest to determine the extent to which 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 neurons innervating the same and different compartments of the ED.
units within and across compartments of ED (Kirkwood and Sears 1978; Nordstrom et al. 1992; Sears and Stagg 1976).

METHODS

Twenty-four experiments were performed on the right ED muscle in nine healthy human volunteers (5 women, 4 men, ages 21–40 yr). 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. Details of the experimental arrangement are presented in Keen and Fuglevand (2003). Briefly, subjects were seated in a dental chair with their right elbow and wrist supported on a horizontal platform. The wrist was stabilized in a position midway between full supination and full pronation by padded vertical posts placed on either side of the distal forearm and on the dorsal and palmar aspects of the hand. The metacarpalphalangeal joints were maintained at a joint angle of ~90° by metal cuffs around the proximal interphalangeal joints that were attached to separate force transducers with relatively in-extensible string. The metal cuffs were individually fitted for each digit. The length of each piece of string was adjusted at the beginning of the experiment so that each digit was preloaded in this flexed position with a force of ~2 N.

Force and electromyographic recording

Extension force of the digits was measured by four force transducers (Grass Instruments, Warwick, RI, 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 (~1000; World Precision Instruments, Sarasota, FL) and displayed on oscilloscopes.

Motor-unit action potentials were recorded with tungsten microelectrodes inserted into ED (Frederick Haer and Co., Bowdoinham, ME, 1- to 5-μm tip diameter, 5- to 10-μm uninsulated length, 250-μm shaft diameter, ~200 kΩ impedance at 1,000 Hz after insertion). Surface electrodes (4 mm diam 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 to record the activity of separate motor units on each electrode. Weak electrical stimulation was used initially to verify microelectrode placement in target compartments of ED based on the relative magnitudes of the forces evoked on each finger (Keen and Fuglevand 2003). Such intramuscular stimulation in ED causes force to develop predominately on one digit only (Keen and Fuglevand 2003). Furthermore, we have shown previously, using intraneural stimulation of single motor axons, that individual ED motor units develop force almost exclusively on single digits (Keen and Fuglevand 2001). Therefore motor units recorded at an intramuscular electrode site that evoked force on a particular digit were likely primarily confined to the affiliated compartment. In some cases, it is likely that electrodes were placed into extensor digitii minimi (EDM), a thin muscle that inserts on the second metacarpal bone and thus innervated by the median nerve, and thus it is likely that the muscle recorded from belonged to EDM. After electrical stimulation, electrodes were connected to differential amplifiers and the intramuscular electromyographic (EMG) signals were amplified (~1000), band-pass filtered (0.3–3 kHz; Grass Instruments), and displayed on oscilloscopes.

Protocol

Subjects performed low-force isometric extension of all four fingers to ensure that ED was activated. The microelectrodes were gently manipulated during the contraction until action potentials of motor units could be clearly identified on each electrode. Once different motor units were identified on the two electrodes, subjects sustained weak contractions of ED such that both units remained active. During the contractions, the forces exerted by individual fingers were not specified; rather, subjects were instructed to maintain the discharge of the two units at low rates while also keeping some level of tension on each finger. Intramuscular EMG signals were recorded for 3 min 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 min 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 reinsetion at a new site. Electrical stimulation was performed to ascertain the compartment location of the electrode when the electrode position was changed. Successive trials were performed for ±2 h. Extension force of each finger and intramuscular EMG signals were digitally sampled at ~2 and 18.5 kHz, respectively, using the Spike2 data-acquisition and analysis system (Cambridge Electronics Design, Cambridge, UK).

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 even 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. Cross-correlation histograms had 1-ms bin widths and included periods 100 ms before and 100 ms after the discharge of the reference unit. A peak in the cross-correlation histogram around time 0 represents the synchronous firing of the two units greater than expected due to chance. 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 was calculated as the mean count in the first and last 60 ms of the cross-correlogram. A rise in the cusum near time 0 was used to delineate the 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). The magnitude of the peaks in the cross-correlograms were quantified as number of counts within the boundaries of the peak above the baseline mean 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).

When cross-correlograms did not exhibit clear peaks, the method described in the preceding text for identifying the region of the histogram for calculation of CIS was not reliable. Therefore for cases of nonsignificant peaks in the cross-correlogram, CIS was automatically calculated for an 11-ms region of the cross-correlogram centered at time 0 (Semmler and Nordstrom 1995). The significance of the cross-correlogram peak was determined according to the method described by Schmied et al. (1993). The number of counts in the peak was required to be >3 SDs above the mean count in the off-peak (z score ≥ 1.96) to be considered significant. All CIS values, regardless of the method used to delineate the region of the histogram for calculation of CIS, were included in the analyses. 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 lo-
RESULTS

A total of 272 motor units in ED were recorded that were used to generate 145 cross-correlation histograms. In 17 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 ± 2.0 Hz, and the mean number of events used to generate the cross-correlograms was 1,864 ± 836.

Four examples of cross-correlograms are shown in Fig. 1. The labels at the top of the figure indicate the compartments within which each of the microelectrodes was located. Substantial synchrony was found for the pair of units both located in the D3 compartment with a CIS value of 0.76 (Fig. 1B). A significant degree of synchrony was also observed for a D3–D4 pair of units with a CIS value of 0.63 (Fig. 1C). However, little synchrony was found when the two electrodes were in nonadjacent compartments i.e., D3–D5, (Fig. 1D) or in the neighboring compartments of D2 and D3 (Fig. 1A) with CIS values of 0.22 and 0.28, respectively.

Of the total of 145 cross-correlograms, 84 had significant peaks. The duration of the synchronous peak, assessed from the cusum, was on average 9.9 ± 2.6 ms for those cross-correlograms that had a significant peak. The average CIS for all pairs of ED motor units (including those with nonsignificant peaks) was 0.57 ± 0.31. The mean CIS values for motor-unit pairs recorded both within and across compartments are shown in Fig. 2. Eighty motor-unit pairs in total were recorded from within the same compartment (Fig. 2, ■). 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 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 three pairs of motor units were recorded in nonadjacent 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 three pairs of motor units was low at 0.14 ± 0.07.

The mean CIS value for all 80 intra-compartment motor-unit pairs was 0.7 ± 0.3 (Fig. 3). In comparison, the mean CIS value for the 65 extra-compartment motor-unit pairs was 0.4 ±
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 subsets of motor neurons innervating specific finger compartments.

0.22, which was significantly smaller \( P < 0.001 \) than the CIS values for intra-compartment motor-unit pairs.

In the present study, the overall mean CIS value for all pairs of motor units in the extrinsic hand muscle ED was 0.57. This value is comparable to the mean CIS values of 0.40 reported for ED motor units by Schmied et al. (1993) and 0.47 for extensor carpi radialis units (Schmied et al. 1994). These CIS values for forearm muscles are not less than, and in some cases slightly greater than, mean CIS values reported for first dorsal interosseus (0.46, Nordstrom et al. 1992; 0.35, Semmler and Nordstrom 1995). Consequently, the magnitude of motor-unit synchrony is not obligatorily greater in intrinsic hand muscles than in more proximal muscles.

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 (Buys et al. 1986; Cheney and Fetz 1985; Fetz and Cheney 1980; McKiernan et al. 1998) 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,b; Gibbs et al. 1995; Huesler et al. 2000). In general, the amount of synchrony for motor-unit pairs residing in the same muscle is usually about twice as great compared with motor-unit pairs in different hand muscles (Bremner et al. 1991b; Huesler et al. 2000). 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 suggests that the extent of shared last-order inputs onto motor neurons supplying different compartments of a multi-tendoned hand muscle is roughly similar to the common input across motor neurons innervating separate hand muscles.

Consistent with previous observations (Bremner et al. 1991b), the magnitude of synchrony was shown in the present study to decline with increasing separation between pairs of units. For example, as shown in the bottom row of the matrix depicted in Fig. 2, the mean CIS for pairs of units in the same compartment \( (D5–D5) \) was about twice that for pairs of units in residing in neighboring compartments \( (D4–D5) \), and was about five times greater than that for pairs of units located in nonadjacent compartments \( (D3–D5) \). Interestingly, Kilbreath and Gandevia (1994) demonstrated a similar pattern in the degree of coactivation across compartments of multi-tendoned finger flexors when human subjects attempted to move indi-

FIG. 3. Mean \((±SD)\) CIS for all intra-compartment motor-unit pairs (●) and extra-compartment pairs (∆) of ED. The mean CIS value \((0.7 ± 0.3)\) for the 80 motor-unit pairs within a single compartment was significantly greater \((P < 0.001)\) than the mean CIS value \((0.4 ± 0.22)\) for the 65 motor-unit pairs that resided in different compartments. Therefore last-order projections appear to predominantly supply subsets of motor neurons innervating specific finger compartments.

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vidual digits. The correspondence between the pattern of inadvertent activity in muscle compartments inserting into digits not intended for movement (Kilbreath and Gandevia 1994) and the distribution of synchrony across motor units residing in different compartments of multi-tendoned muscles (Bremner et al. 1991b; present study) is consistent with the idea that divergence of the descending commands may limit the ability to move the fingers independently.

Bremner and colleagues (1991b) also observed a tendency for greater synchrony among motor units in more medial (ulnar) than lateral (radial) muscles or muscle compartments. Motor units residing in muscles inserting into the little finger, however, were not evaluated in that study. We have extended those findings (Bremner et al. 1991b) to show that the magnitude of synchrony within and across compartments of ED does not necessarily continue to increase for more medially situated compartments but rather reaches its apogee with the D4 compartment. The largest value of intra-compartment synchrony was for D4 motor units and the least synchrony was for D2 units (Fig. 2). Moreover, the degree of extra-compartment synchrony for D3/D4 motor-unit pairs was not less than (and indeed was slightly greater than) synchrony for D4/D5 pairs. Also, extra-compartment synchrony between D4 units and units in either of the neighboring compartments (D3 or D5) was significantly greater than extra-compartment synchrony for D2/D3 motor-unit pairs.

These findings suggest 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 with inputs that primarily target motor neurons supplying other compartments. Consequently, when attempting to activate motor neurons innervating a compartment of ED, particularly the D4 compartment, branches from last-order inputs may activate motor neurons innervating muscle fibers in neighboring ED compartments. If unopposed by antagonistic muscle activity, this may result in some extension of other digits when attempting to extend just one digit. Indeed, studies that have measured the relative independence of finger movements in humans (Häger-Ross and Schieber 2000; Robinson and Fuglevand 1999) have found that fingers do not move independently of one another. Lack of independence in finger movements does not appear to be caused primarily by biomechanical factors (Keen and Fuglevand 2003; Kilbreath and Gandevia 1994). Furthermore, the least-independent finger movement is extension of D4, whereas extension of D2 is the most-independent movement compared with extension of the other fingers (Häger-Ross and Schieber 2000; Robinson and Fuglevand 1999).

These behavioral findings roughly coincide with the general pattern of motor-unit synchrony observed across compartments of ED in the present study.

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.

GRANTS

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