Discharge Variability of Motor Units in an Intrinsic Muscle of Transplanted Hand

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Introduction

Hand transplantations have been performed on only a few individuals, all of whom are currently healthy with viable grafts, except for the first patient who experienced rejection (Dubernard et al. 2001). Sensorimotor recovery in these patients depends on the nerve regeneration (Owen 2001) that occurs in transplanted hands even many years after the trauma (Lanzetta et al. 2005).

We recently reported an electromyographic (EMG) analysis of a reinnervated muscle in one of these individuals (Lanzetta et al. 2005). Measurements made over a period of 2 yr after the operation allowed the assessment of when the axons innervated the muscle fibers of the donor’s hand. The results indicated that motor axons innervated the muscle fibers of a transplanted hand even 22 yr after the amputation. The hand was then revascularized by anastomosing the radial and ulnar arteries and three veins. The median and ulnar nerves were repaired and the remaining more superficial flexor tendons were sutured.

METHODS

The Italian Hand Transplantation Program was approved by the Italian Health Department and the Ethical Committee of the University of Milan–Bicocca. The recipient was a 35-yr-old man who had lost his right hand (dominant) in a farming accident when he was 13 yr of age. The patient underwent a series of routine pretransplant investigations, including an angiogram, computerized tomography scan, muscle and nerve charts, magnetic resonance imaging of the stump, a functional magnetic resonance imaging of the brain, and a comprehensive battery of psychological and clinical tests. The donor was a 43-yr old man who had died from a stroke.

Surgical procedure

The surgical procedure was described in detail previously (Dubernard et al. 1999). The operation lasted 12 h with a total ischemia time of 11 h. Bone fixation of the radius and ulna was achieved by means of compression plates and 4.5-mm screws. Autologous cancellous bone graft from the iliac crest was placed around the osteosynthesis site to improve healing. Most of the deep flexor and all extensor tendons were repaired. The hand was then revascularized by anastomosing the radial and ulnar arteries and three veins. The median and ulnar nerves were repaired and the remaining more superficial flexor tendons were sutured.

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Immunosuppressive regimen

The patient had a mass of 73 kg and was given 250 ml of Dextran 40 before declamping and received 20 ml/h for 7 days. Aspirin 150 mg was administered for 7 days and wide-spectrum antibiotic therapy for 10 days. The induction immunosuppressive protocol consisted of 20 mg of monoclonal antibody anti-CD25 (Baxilimab, Simulect) 2 h before the operation, on day 4 and on day 45 postoperatively, FK506 (tacrolimus, Prograf), adjusted to maintain blood concentration between 15 and 20 ng/ml for the first month, mycophenolate mofetil (Cell Cept 2 g/day), and steroid (prednisone 250 mg on day 1 and rapidly tapered to 20 mg/day). The maintenance therapy consisted of FK506 (blood levels between 5 and 10 ng/ml), mycophenolate mofetil 1 g/day, and prednisone 10 mg/day.

Hand rehabilitation

Physiotherapy began after the swelling subsided and was performed twice daily for 138 days and once daily thereafter as the patient returned to work. The program included standard rehabilitation for flexor and extensor tendons and began with assisted active mobilization of the shoulder and elbow. A static protection splint of the wrist was used during the first week. In the second week, passive mobilization of the wrist and hand was initiated with extension of the wrist and bending of the fingers. This was followed by active-assisted movements and progressed to active bending-extension movements of the wrist (extrinsic muscles) in the fourth week. When performance of active tasks of the fingers and the wrist improved, the rehabilitation focused particularly in increasing tendon gliding, flexor–extensor balance, and grip strength. Eight weeks after the operation, electrotherapy was applied to strengthen the extrinsic muscles in the forearm. Electrical stimulation was performed twice a week for 1 yr. In each session, electrical stimulation was applied to the pronator teres, flexor carpi ulnaris, extensor carpi ulnaris, extensor carpi radialis, anconeus, and extensor digitorum, with 200-µs pulses and the intensity adjusted to activate the whole muscle (clinically judged). The stimulation frequency was 8 Hz for warm up, 35 Hz for tetanic contractions, and 3 Hz for recovery. The tetanic stimulation was delivered for 6 s followed by 8 s of rest, with 20 repetitions in each session. Electrical stimulation was not applied to any of the intrinsic hand muscles.

Experimental procedures

Multichannel surface EMG signals were recorded from the intrinsic muscles of the transplanted hand to evaluate motor unit reinnervation (Lanzetta et al. 2005) and control properties. The first set of recordings was obtained at day 205 (7 mo) postoperatively, followed by a second evaluation at 11 mo and then monthly thereafter, until 10 sessions had been completed. An additional session was performed 4 mo after the 10th session. The muscles investigated were the abductor digiti minimi, abductor pollicis brevis, opponens pollicis, first dorsal interosseous, and first lumbricals, as described in a preliminary study focusing on muscle fiber reinnervation (Lanzetta et al. 2005). The present study reports results from the abductor digiti minimi, which was the only muscle where the discharge of individual motor units could be identified in repetitive sessions.

The skin overlying the muscle was lightly abraded with paste to improve the quality of the skin–electrode contact. A linear array of 16 silver dot electrodes (1-mm diameter, 2.5-mm interelectrode distance) was held over the muscle by an operator who instructed the subject on the movement to be performed and provided resistance for the action. The electrode location and direction were chosen to detect signals showing propagation of motor unit action potentials along the array with minimal shape changes. Surface EMG signals were amplified by a multichannel amplifier (EMG 16, LISiN, Ottino Bioelettronica, Turin, Italy) and band-pass filtered (3-dB bandwidth, 10–500 Hz), sampled at 2,048 samples/s, converted to digital data by a 12-bit A/D converter board, displayed in real time, and stored on a PC for further processing. The EMG signals were processed on-line by a custom-made instrument that generated an analog signal with an amplitude proportional to the number of motor unit action potentials being detected each second. The discharge rate signal was displayed on an oscilloscope for visual feedback to the subject.

The subject was asked to perform three 60-s contractions at maximal effort with a 5-min rest between contractions. He was verbally encouraged to maintain a maximal effort during the contractions. After a 5-min rest, the subject performed three additional 60-s contractions that involved linearly increasing the muscle activity from the minimum to maximum using the visual feedback on motor unit discharge rate. The multichannel EMG signals were recorded during the contractions and during the rest periods.

The action potentials discharged by single motor units were identified off-line from the EMG signal with a decomposition algorithm (Gazzoni et al. 2004). The instantaneous discharge rate of the identified motor units was estimated as the inverse of the interspike interval (ISI). The variability in ISI in each 2-s epoch was expressed as the coefficient of variation (CV, %) \( C = (\mu/\sigma) \times 100 \), where \( \mu \) is the mean ISI and \( \sigma \) is the SD of the ISI. Although the CV for the ISI is often used as a measure of variability for the discharge of motor units, the neural control signal should be linked to the rate of action potentials rather than to the ISIs (Stein et al. 2005). The variability associated with discharge rate is expressed as the SD of the number of action potentials during a selected interval of time. Therefore the SD of the number of discharges (ND) in time intervals of 2 s was computed as \( SD_{ND} = (\sigma/\mu)\sqrt{T/\mu} \) (Cox and Miller 1965; cited in Stein et al. 2005), where \( T \) is the time interval from which \( SD_{ND} \) is estimated. The CV of the number of discharges in the time interval \( T \) was computed as the ratio (%) between \( SD_{ND} \) and the mean number of discharges in the interval \( T; \mu_{ND} = T/\mu \). High-frequency bursts of action potentials, which included two to six action potentials, were defined as ISIs of <20 ms (Bawa and Calancie 1983).

Statistical analysis

The average discharge rate and the CV for ISI were compared during the first and last 2 s of both the maximal and ramp contractions with paired Student’s \( t \)-test. The associations between the SD of ISI, \( SD_{ND} \), CV for ISI and for the number of discharges, and mean ISI were examined with a linear regression analysis.

High-frequency bursts of action potentials were observed in all recordings. Two-way repeated-measures ANOVA was used to examine instantaneous discharge rate before and after the high-frequency bursts. The factors were the occurrence in time with respect to the high-frequency bursts (pre or post) and the relative lag or lead time of the bursts. When the ANOVA identified a significant effect, post hoc Student–Newman–Keuls (SNK) test was used for pairwise comparisons. Linear correlation analysis was performed between the instantaneous rate of discharges within the bursts.

The significance level was \( P < 0.05 \) and results are reported as mean and SD in the text and mean and SE of the mean in the figures.

RESULTS

The patient could begin to grip objects by the sixth postoperative month. This action did not involve activation of the intrinsic muscles and was mainly accomplished by wrist extension and finger bending through extrinsic muscles. The gripping ability was later followed by reinnervation of the intrinsic muscles. Twelve months after the transplant, the patient was able to perform many activities of daily living, such as driving a car and riding a bike. The activity of the intrinsic muscles was limited to very small forces correspond-
ing to surface EMG signals that consisted of only a few active motor units. Only two motor units could be identified concurrently in the abductor digiti minimi, three in the abductor pollicis, and one each in the opponens pollicis, the first dorsal interosseous, and the first lumbricalis muscles.

Motor unit recordings

Analysis of the motor unit discharge pattern was limited to the abductor digiti minimi, where one motor unit was identified in all sessions after the first sign of reinnervation. Motor unit activity in the abductor digiti minimi was observed over 11 mo postoperatively, as previously reported (Lanzetta et al. 2005), and results on motor unit discharge patterns were obtained from 10 experimental sessions. A total of 14 maximal contractions and 13 ramp contractions were analyzed from the 10 sessions. This set of contractions was not the same as those analyzed by Lanzetta et al. (2005) due to the more stringent criteria on signal quality adopted in the current study for assessment of the discharge pattern. The contractions not included in the current analysis had lower EMG signal quality due to movement artifacts, power line interference, and other noise sources. At least one maximal and one ramp contraction were analyzed from each session. One main motor unit was identified in each analyzed contraction and its complete discharge pattern was extracted from the EMG signal. The action potentials of this motor unit were clearly identifiable (Fig. 1) for the entire range of forces analyzed. Additional smaller motor units were occasionally identified, for a maximum of two concurrently active motor units, but were excluded from the analysis due to the relatively low signal-to-noise ratio of their action potentials and their appearance in only some of the experimental sessions after reinnervation.

Figure 1 shows signals recorded during a maximal contraction and the extraction of individual motor unit action potentials from this recording. The detected action potentials propagated along the direction of muscle fibers, indicating that the electrode array was aligned to the muscle fibers. The average velocity of propagation of the action potentials for all motor units, estimated as described by Farina et al. (2001), was 4.6 ± 1.3 m/s, which is similar to that observed in able-bodied persons in the same muscle (Farina et al. 2004). Thus it is unlikely that the recorded action potentials were cross talk from other muscles (Farina et al. 2002).

Although there was a large variation in the amplitude of the action potentials detected in different sessions, the correlation coefficient between the average action potentials of the analyzed motor units across sessions was very large (range 0.87–0.98). Because of this high similarity in shape and similar characteristics in discharge over the sessions, it is likely that the same motor unit was detected in all sessions.

The EMG activity was continuously monitored during the 5-min periods between contractions as the subject rested. No action potentials were identified and the amplitude of the EMG signals was within the noise level during the rest periods. Thus no spontaneous activity or muscle hyperactivity was detected in the abductor digiti minimi muscle.

Discharge characteristics

Discharge rate was averaged across motor units at the beginning (first 2 s) and at the end (last 2 s) of both the maximal and the ramp contractions. It decreased from 27.1 ± 8.4 to 17.2 ± 2.9 pps during the maximal contractions (t-test, P < 0.001; Fig. 2A). Conversely, it increased from 17.4 ± 4.3

FIG. 1. Representative signals from the abductor digiti minimi muscle of the transplanted hand. A: 15 bipolar EMG signals were derived from a linear array of 16 electrodes located along the estimated fiber direction. B: one of the 15 bipolar signals is shown on a more compressed timescale. C: superimposed action potentials from channel 5 (top) to channel 1 in A show its propagation along the muscle fibers. The similarity of the shape and amplitude of the action potentials indicates that they belong to the same motor unit.
to 22.1 ± 5.0 pps during the ramp contractions (t-test, P < 0.05; Fig. 2B). There was a trend toward a significantly greater discharge rate at the beginning of the maximal contractions compared with the end of the ramp contractions (P = 0.07).

The interspike interval variability did not differ at the beginning and end of the maximal contractions (average over all 2-s intervals during the 60-s contraction, n = 14 maximal contractions: 36.8 ± 10.8%) or for the ramp contractions (n = 13 ramp contractions, 35.9 ± 7.4%) and did not differ between the two tasks (P = 0.86). The SD of the ISI, which is an index of the absolute variability in discharge rate, increased with the mean ISI with a similar slope of the linear regression for the maximal (0.49 ± 0.09; Fig. 3A) and ramp contractions (0.43 ± 0.1; Fig. 4A) (P = 0.19). There was a weak association between ISI variability and mean ISI during the maximal contractions (R² = 0.23, P < 0.001; Fig. 3B), but not during the ramp contractions (R² = 0.04; Fig. 4B).

The variability in discharge was also analyzed with respect to the number of action potentials in 2-s intervals, which characterizes the variability in the drive to the muscle in a given time interval (Stein et al. 2005). This measure of variability reflects the variability in the neural control signal

FIG. 2. Range of motor unit discharge rates. A and B: discharge rate of the detected motor units during the maximal (A) and ramp (B) contractions. Each dot corresponds to the average discharge rate over a 2-s interval for a single motor unit. Fourteen and 13 motor units are represented in A and B, respectively.

FIG. 3. Variability in interspike interval (ISI) during the maximal contractions. A: SD of the ISI vs. mean ISI for each of the motor units (n = 14) detected during the maximal contractions. B: coefficient of variation (CV) for the ISI relative to mean ISI. C: SD of the number of discharges (ND) within 2-s intervals as a function of mean ISI. D: CV for the number of discharges within 2-s intervals vs. mean ISI. Each data point corresponds to average over 2-s intervals.
relative to the number of action potentials discharged per unit time. With constant ISI variability, $SD_{ND}$ theoretically decreases with the square root of the mean ISI. Because the SD of the ISI tended to increase with increasing mean ISI (Figs. 3B and 4B), however, $SD_{ND}$ did not depend on the mean ISI during either the maximal contractions ($R^2 = 0.02$; Fig. 3C) or the ramp contractions ($R^2 = 0.03$; Fig. 4C). Thus although the SD of the ISI was linearly related to the mean ISI (Figs. 3A and 4A), the absolute variability in the number of action potentials that were discharged by the motor neurons in a constant time interval did not depend on mean discharge rate. With constant $SD_{ND}$, the CV for the number of action potentials in a given time interval should be linearly related to the mean ISI (Stein et al. 2005). Accordingly, a linear relation between the CV for number of action potentials and mean ISI was observed for both contractions (maximal contractions: $R^2 = 0.50$, $P < 0.001$; Fig. 3D; ramp contractions: $R^2 = 0.24$, $P < 0.001$; Fig. 4D).

**High-frequency bursts of activity**

The instantaneous discharge rate during both types of contractions occasionally included brief increases to very high values. Figure 5 shows examples in which there were many discharges with instantaneous rates $>50$ pps. The high-frequency bursts, defined as two or more action potentials with ISIs $<20$ ms (Bawa and Calancie 1983), were distributed approximately uniformly in the 10 sessions. Figure 6 shows representative examples of the types of high-frequency bursts identified from this patient. Up to six action potentials at $<20$ ms were identified, whereas able-bodied individuals produce a maximum of only two consecutive action potentials closer than $20$ ms (Bawa and Calancie 1983).

The number of action potentials in the high-frequency bursts was relatively small and corresponded to 3.5% of the total number of detected action potentials in both contraction types (Table 1). Assuming a Gaussian distribution of ISIs, an average discharge rate for the entire set of contractions of about 20 pps, and a CV for the ISI of about 35%, the theoretical probability for an instantaneous discharge rate to exceed 50 pps is about 4%. Thus the number of high-frequency bursts was consistent with the high variability of the ISI.

Further analysis of the high-frequency bursts with fewer than five action potentials indicated that the instantaneous discharge rate for the first ISI did not differ among bursts with two, three, or four potentials. In addition, the subsequent ISIs in the bursts with three and four potentials did not occur at a statistically different rate (Fig. 7) and there was no correlation between the instantaneous rates within the bursts. Moreover, there was no difference in the average discharge rate of the four ISIs that preceded and followed the bursts with two to four potentials (Fig. 7). A systematic adjustment, however, was evident in the ISIs immediately before and after these bursts because they had the lowest instantaneous discharge rate among the four preceding and the four following ISIs (maximal contractions: ANOVA: $F = 6.5$, $P < 0.001$; SNK: $P < 0.05$;
DISCUSSION

The variability in discharge rate of motor units in an intrinsic muscle of a transplanted hand was analyzed during maximal and ramp contractions with a multichannel surface EMG. Although the average discharge rates were within the physiological range observed in able-bodied individuals, discharge variability was much greater and included high-frequency bursts of activity.

Individual motor units are usually investigated in vivo with intramuscular recordings. However, invasive electrophysiological techniques cannot be applied in hand-transplanted persons due to the high risk of infection. Highly selective surface EMG recordings were used in the current study and were capable of detecting the action potentials discharged by single motor units even during maximal contractions due to a reduction in the number of functioning motor units in this muscle. The criteria for the single motor unit recordings were the absence of sudden changes in action potential shape and the presence of a continuous discharge pattern.

The muscle fibers of a donor’s hand are slowly reinnervated by the axons of the recipient (Lanzetta et al. 2005). The current study was based on the action potentials discharged by the dominant motor unit that was identified in each contraction from surface EMG recordings. Smaller action potentials, corresponding to either small or deep motor units, were also occasionally identified but overall the number of detected motor units did not change substantially over the course of the study and a maximum of two motor units was concurrently detected. Prolonged axotomy does not compromise the number of muscle fibers innervated by each axon (Fu and Gordon 1995). Although axonal regeneration does not appear to be impaired with prolonged axotomy (Kobayashi et al. 1997), fewer functional motor axons reach a denervated muscle (Fu and Gordon 1995). A reduction in the capacity to restore a functional neuromuscular junction (Kobayashi et al. 1997) may explain the absence of an increase in number of active motor units during the study. Most functional tasks could be performed by the subject with the use of extrinsic muscles.

The average minimal and maximal discharge rates during maximal and ramp contractions were similar to those observed in hand muscles of able-bodied persons (Bellemare et al. 1983;
The average discharge rate decreased during the maximal contractions, as observed in able-bodied persons (Bigland-Ritchie et al. 1986). These observations suggest the presence of muscle afferent feedback to the analyzed motor neurons during the contractions because the discharge rate of motor neurons during maximal efforts in the absence of afferent feedback is lower than that observed in normally innervated motor units and does not decrease with prolonged activation (Gandevia et al. 1990), contrary to the current observations.

The decrease in discharge rate can be partly attributed to the adaptation of motor neuron discharge rate (Nordstrom et al. 2007), a change in afferent input [e.g., increase in group III and IV muscle afferent activity (Bigland-Ritchie et al. 1986) or a decrease in the discharge rate of muscle spindle afferents (Macefield et al. 1991)], or a reduction in descending drive (Hunter et al. 2006; Todd et al. 2003). Because a direct measure of afferent input to the analyzed motor neurons is not possible, an influence of afferent input on the observed variability in discharge rate cannot be excluded. The visual feedback provided to the subject during the ramp contractions enhanced the control of motor unit discharge, as observed in able-bodied persons (Farina et al. 2004). The combined observations for the maximal and ramp contractions indicate that the subject could voluntarily modulate motor unit discharge rate over the entire physiological range.

Although the average discharge rates were similar to those recorded in able-bodied persons, the variability in interspike interval observed during the voluntary contractions performed with the abductor digiti minimi muscle in the transplanted hand was greater than that reported previously (Person and Kudina 1972). Although the greater variability might be attributed to poor control of motor unit discharge based on the visual feedback during the ramp contractions, the subject exerted the maximal force without modulation of effort during the maximal contractions and the amount of variability was similar to that measured during the ramp contractions.

The variability in discharge rate was quantified at various ISIs because an accurate measure of variability can be obtained only by measuring the discharge-rate variability for the same motor unit over a range of ISIs (Barry et al. 2007). The absolute variability in discharge rate was linearly related to the ISI, but the slope of the regression line (0.49 for maximal contractions) was larger than that reported previously for hand muscles in healthy subjects. For example, Barry et al. (2007) found a slope of 0.38 for the first dorsal interosseus of young adults. Similarly, the CV for ISI was about 25% at recruitment and decreased to about 14% with an increase in discharge rate in young adults (Barry et al. 2007).

The variability in discharge rate is due to synaptic noise and its interaction with the time course of the postspike afterhyperpolarization (AHP) phase of the motor neuron (Calvin and Stevens 1967; Matthews 1996; Stein et al. 2005). The large variability in discharge rate observed in this patient might be caused by greater synaptic noise due to larger synaptic input received by the motor neurons (Berg et al. 2007), indicating that the motor neurons innervating the transplanted hand may require greater synaptic input to reach voltage threshold (Cope et al. 1986). Increase in synaptic input to the motor neuron

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<th>Number of APs/Burst</th>
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%, percentage of APs in the bursts relative to the total number of APs recorded during the contractions.
depends on the balanced increase in both excitation and inhibition (Berg et al. 2007). The balanced increase in these two inputs increases discharge variability by increasing motor neuron conductance (i.e., the motor neuron becomes leakier to electric current) and the fluctuations in the membrane potential (Berg et al. 2007). The consequent synaptic noise varies with activity level and consists of synaptic transients in the high-conductance state of the motor neuron. A possible source of these transients is the high incidence of uncorrelated excitatory and inhibitory synaptic events.

Nonetheless, axotomy can shorten the duration of the AHP (Hochman and McCrea 1994; Kuno et al. 1974a,b), which could increase the variability in discharge rate (Matthews 1996; Powers and Binder 2000). A reduction in the duration of the AHP is associated with an increase in the SD of the ISI for low discharge rates (long ISIs) (Powers and Binder 2000). However, the duration of the AHP has a relatively minor influence on the SD of the ISI for high discharge rates (brief ISIs) (Fig. 3 in Powers and Binder 2000). Because the level of variability during long ISIs was greater for the patient (Figs. 3 and 4) compared with able-bodied persons (Barry et al. 2007), it seems that the fluctuations in membrane potential due to enhanced synaptic noise was a major contributor to the greater variability in motor unit discharge rate.

The high variability in ISI resulted in the occasional occurrence of high-frequency bursts of action potentials. Although the number of bursts was rather limited, the pattern was more pronounced than that observed in able-bodied persons. When an individual performs either a steady contraction or one in which the force increases gradually, motor units in some muscles discharge pairs of action potentials with an ISI <20 ms; this is often referred to as double discharges or a doublet (Bawa and Calancie 1983; Christie and Kamen 2006; Garland and Griffin 1999). Doublets seem to be related to intrinsic properties of the motor neuron itself (Kudina and Alexeeva 1992). A motor neuron may present a state of increased depolarization, or delayed depolarization, that occurs during the falling phase of the action potential. The delayed depolarization is proposed to result from an antidromic invasion of the dendrites (Granit et al. 1963). The motor neuron is more susceptible to slight increases in synaptic input during the delayed depolarization and can thus produce a second action potential. The occurrence of the second action potential, however, is followed by a period of hyperpolarization that results in an increased ISI (Calvin and Schwindt 1972). The occurrence of more than two action potentials at very short distance is very unlikely because of the period of hyperpolarization following doublets. Bursts of three potentials at distance <20 ms in healthy humans were indeed observed only during dynamic contractions when the synaptic input may present large and rapid variations (Garland et al. 1996; Van Cutsem et al. 1998).

In the current study, the percentage of action potentials included in the high-frequency bursts was consistent with the number of ISIs <20 ms, as theoretically predicted by considering the observed variability in ISI. It is likely that larger synaptic noise and changes in the time course of the postspike AHP made the presence of repetitive potentials at short distance between each other more likely than in healthy subjects.

**FIG. 7.** Instantaneous discharge rate within the high-frequency bursts. Mean (±SE) instantaneous discharge rate for bursts of 2 (A, B), 3 (C, D), and 4 (E, F) discharges in the maximal effort (A, C, E) and ramp contractions (B, D, F). The 4 discharges immediately before (p1–p4) and those immediately after (P1–P4) the high-frequency bursts are shown and further analyzed (see text for statistical analysis). D: second discharge in bursts of 2 action potentials; T2 and T3, second and third discharges in bursts of 3 action potentials; Q2, Q3, and Q4, second, third, and fourth discharges in bursts of 4 action potentials.
The high-frequency bursts were observed over the entire 16 mo of assessment.

In summary, motor units in the abductor digiti minimi muscle of a transplanted hand discharged action potentials with a variability that was greater than that in able-bodied persons, as may result from larger synaptic noise and changes in the postspike AHP.

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REFERENCES