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CENTRAL NERVOUS PATHWAYS UNDERLYING SYNCHRONIZATION OF HUMAN MOTOR UNIT FIRING STUDIED DURING VOLUNTARY CONTRACTIONS

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SUMMARY

1. Motor unit firing has been studied during weak voluntary isometric contractions with pairs of needle electrodes in normal human subjects.

2. Pre- and post-stimulus time histograms of the firing time of firing of one event unit before and after the time of firing of another reference (stimulus) unit showed a clear central peak, indicative of synchronization.

3. Synchronization was seen in all the muscles studied. The mean strength of synchronization, expressed as the number of concomitant discharges of the two units as a proportion of the number of stimulus unit discharges, was 0·095 extra event unit spikes/reference unit spike (range 0·042–0·28) for first dorsal interosseous muscle, 0·016 extra event unit spikes per reference unit spike (range 0–0·043) for medial gastrocnemius and 0·056 extra event unit spikes per reference unit spike (range 0·016–0·079) for tibialis anterior.

4. The mean duration of synchronization was 11·3 ms (range 5·0–21·0 ms) for first dorsal interosseous, 10·3 ms (range 3·5–21·7 ms) for medial gastrocnemious and 13·5 ms (range 3·0–25·0) for tibialis anterior.

5. Seven patients with radiographically and clinically identified central strokes were studied while they made weak voluntary isometric contractions. The duration of synchronization was significantly prolonged compared to that found in normal subjects. In these stroke patients the mean duration of synchronization on the affected side was longer than that seen in the normal subjects, and in first dorsal interosseous muscle was 35·4 ms (range 12·0–65·0 ms), in medial gastrocnemius was 21·3 ms (range 4·0–43·0 ms) and in tibialis anterior was 28·8 ms (range 14·0–49·0 ms).

6. The mean strength of synchronization of motor unit discharge was found to be greater in the stroke patients than that seen in the normal subjects for first dorsal interosseous muscle (0·161 extra event unit spikes per reference unit spike, range 0·017–0·391) and for medial gastrocnemius (0·030 extra event unit spikes per reference unit spike) but only significantly so when pooled data was compared. There was no difference in the strength of motor unit synchronization in tibialis anterior between stroke patients and normal subjects.

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7. Broad duration synchronization among first dorsal interosseous motor units was also found in a pateint with a rostral cervical spine lesion (total duration range 43–46 ms; $n = 2$), but not in a patient with a caudal (thoracic) spinal lesion. Broad duration synchronization was also found in a patient with untreated idiopathic Parkinson's disease (range 37–45 ms; $n = 2$) and in a patient with a cerebellar haematoma (range 19–28 ms; $n = 2$) but not in a patient with Huntington's chorea (range 9–20 ms; $n = 2$).

8. Normal subjects were asked to isometrically co-contract two muscles; the firing of a motor unit in each muscle was studied. Synchronization of motor unit firing was always found between muscles defined as anatomical antagonists. The strength of synchronization between first dorsal interosseous muscle and second palmar interosseous muscle ranges from 0·02–0·03 extra event spikes per reference antagonist unit spike and ranges from 0·02–0·03 extra event unit spikes per reference antagonist unit spike between medial gastrocnemius and tibialis anterior ($n = 13$). Synchronization was also found between motor units in adjacent intrinsic hand muscles and was stronger than between more widely separated intrinsic hand muscles.

9. The results are interpreted in terms of the presynaptic nervous pathways to the motor units studied which produced the observed short term synchronization during voluntary contractions in normal subjects. It is proposed that descending pathways of cortical origin, including branched stem corticospinal axons, are important in the generation of short-term synchronization. Following contralateral cortical lesions and rostral spinal lesions, it is proposed that synchronization of spinal presynaptic neurones including interneurones produced the observed broad duration synchronization of motor unit discharge.

INTRODUCTION

Motor units of mammalian muscles discharge together more than would be expected by chance alone over a brief time period (Dietz, Bischofberger, Wita & Freund, 1976; Sears & Stagg, 1976; Datta & Stephens, 1980). This short-term synchronization of motor unit discharge has been described by an explicit model whereby the time course of the synchronization in intercostal motoneurones of the anaesthetized cat has been related to the time course of EPSPs in presynaptic branched stem axons and the properties of the motoneurone in translating synaptic depolarization into discharge (Kirkwood & Sears, 1978). This model has been proposed as valid for the short-term synchronization seen in first dorsal interosseous motor units during voluntary contractions in conscious man (Datta & Stephens, 1983, 1990).

In the decerebrate or lightly anaesthetized cat, synchronization has been shown to be stronger between intercostal motoneurones in adjacent thoracic segments than between more widely separated segments (Kirkwood, Sears, Stagg & Westgaard, 1982*a*). Similarly, the duration of synchronization has been shown to be much prolonged following a spinal section but not after dorsal root section (Kirkwood, Sears & Westgaard, 1984). These observations led those authors to propose that the short-term synchronization they observed was generated predominantly by branched stem axons which transmit the respiratory drive, some of which are the bulbospinal neurones.

The strength of synchronization seen during quiet tidal breathing in intercostal motoneurones in the anaesthetized cat and in a conscious human subject (Sears & Stagg, 1976) is weak, and similar to that seen during reflex hypercapnic obstructed breathing in sternocleidomastoid motor units of conscious human subjects (Adams, Datta & Guz, 1989). In contrast the strength of synchronization during voluntary obstructed breathing is much stronger, and as strong as that seen in a hand muscle during voluntary isometric contractions (Datta & Stephens, 1980, 1990; Adams *et al.* 1989). These results led to the hypothesis that the branched stem presynaptic inputs to motoneurones during voluntary contractions are of cortical origin. In this study we have examined the central nervous pathways underlying the synchronization of motor unit firing during voluntary contractions, by studying synchronization within and between different muscle groups and comparing the results obtained in normal subjects with those obtained in patients with identified central nervous lesions.

Preliminary accounts of these experiments have been reported to the Physiological Society (Datta & Stephens, 1980; Datta, Fleming & Stephens, 1985*a*, *b*) and to the American Society for Neuroscience (Datta, Fleming, Hortobagyi & Stephens, 1985*c*).

METHODS

All experiments were performed with Local Ethical Committee approval on subjects who had given informed consent. Recordings were made on eighteen normal subjects (one female) aged 18–33 years and from seven patients (three female) aged 42–72 years who had suffered a stroke between 3 and 32 weeks earlier. The only entry criterion applied was that the subject/patient should be willing and able to make a voluntary contraction of the muscle under study. The anatomical location of the stroke was determined clinically and confirmed by computerized axial tomography. Five lesions were infarctions in the parietal lobes of the cerebral hemispheres, one was a parietal lobe haemorrhage and the last a brain stem infarction. Full clinical details of the patients are given in Table 1. Recordings were also made from a 61-year-old female patient with newly diagnosed, untreated Parkinson's disease, a 42-year-old male patient with Huntington's chorea and a 65-year-old male patient who had sustained a cerebellar haemorrhage 7 months previously confirmed by computerized axial tomography. Two male patients with spinal lesions were studied. One, aged 72, had a cervical spinal lesion from C6–T1, due to a malignant infiltration from prostatic carcinoma. The other, aged 27, had a spinal abscess and subsequent antibioma excised at the level of T7. In all patients there was residual function such that they were able to make steady voluntary isometric contraction. Clinical signs of lower motoneurone dysfunction were absent. Recordings from patients were made on the ward, while those from normal subjects were made in the laboratory.

Intrinsic hand muscle motor unit recording

The subject was comfortably seated, with the hand and forearm supported on a table. The hand was immobilized in a specially constructed Perspex frame, with the thumb fully abducted and extended. Stops were placed beside the appropriate proximal interphalangeal joint so that recordings were made during weak isometric contractions. A strain gauge (Statham, type UC3 with UL4-2 loadcell) was placed on the lateral aspect of the proximal interphalangeal joint of the index finger so that unit recruitment thresholds could be recorded in the normal subjects. Concentric monopolar needle electrodes (type EN/01, Medelec Ltd) were inserted into the muscle or muscles under study to record the electromyogram (EMG) discharge of a motor unit. Each electrode was positioned to record the EMG activity of one unit only. The EMG of two motor units A and B were amplified and heavily filtered (−3 dB at 2 kHz) to improve unit isolation (Medelec, MS6). EMG was recorded on an FM tape-recorder (Racal Store 4DS; bandwidth 0–5 kHz) for subsequent analysis.

The subjects were requested to make a weak contraction for 5–10 min, such that one unit (B) discharged at 10 impulses s^{-1}. They were aided in this by auditory feedback of unit activity and visual feedback of a ratemeter display.

Leg muscle motor unit EMG recording

The general recording arrangements were similar to that for the hand as described above. The subject was seated in a chair and had the knee flexed at 135 deg, with the leg and foot supported in an immobile rigid frame constructed for the purpose. Subjects were asked to maintain a weak isometric dorsiflexion when recordings from medial gastrocnemius or soleus were made and a weak

TABLE 1. Clinical details of patients with stroke

Patient	Sex	Age (yr)	Brain CT appearance	Lesion-study interval (weeks)	Affected 1DI power (MRC grade)	Increase in upper limb tone	Upper limb reflexes	Median (range) duration of synchrony (ms)
G.B.	F	70	Normal (left pontine haemorrhage)	26	4	Mild	++	21 (18–40)
J.T.	M	69	Right parietal infarction	23	4	Moderate	++	19 (12–35)
T.T.	M	56	Right parietal haemorrhage with surrounding oedema	5	4	Mild	+	53 (25–53)
H.W.	M	69	Right parietal infarction	10	3+	Mild	+++	51 (32–65)
S.A.	M	41	Right parietal infarction	24	3+	None	+	26 (21–38)
E.W.	F	70	Right temporal and parietal infarction	21	4	Moderate	++	41 (37–45)
D.S.	F	71	Right parietal infarction	3	4	Mild	++	38 (16–65)

The clinical diagnosis of patient G.B. (confirmed by an independent consultant neurologist) is given in brackets beside the CT scan appearance. +, ++ and +++ indicate decreased, normal and increased strength of reflex respectively.

isometric plantar flexion when recordings from tibialis anterior were made. Pairs of long concentric monopolar needle electrodes (Medelec Ltd, Type ENS/2) were then inserted into the muscle to obtain recordings of pairs of motor units A and B, one from each electrode. Unit B was maintained at 10 impulses s^{-1} by the subject.

Motor unit EMG analysis

The waveform of each of the two unit action potentials A and B was delayed by 5 ms and visualized on two channels of an oscilloscope screen (Tektronix, 565). The top channel of the oscilloscope was triggered by pulses derived from unit A and the bottom channel by unit B action potential-derived pulses that had been passed (undelayed) through window discriminator circuits (Neurolog). For the purpose of this study, unit action potentials were selected and analysed if they met the criteria of Adams *et al.* (1989).

Pre- and post-stimulus time histograms (PPSTH) (bin width 391–1000 μs, minimum 1000 sweeps) of the firing of the event unit A before and after the firing of the reference (stimulus) unit B were constructed. Their cumulative sums (Ellaway, 1977) were computed with an analog computer and displayed above to derive the duration and strength of synchronization. The duration of synchronization was obtained from the time between the inflexions in the cumulative sum (cusum) display. The strength of synchronization (e/T) was defined in this study as the total number (above control) of the extra unit A discharges for the duration of synchronization (e)

expressed as a proportion of the total number of reference (stimulus) unit B discharges (T) (Datta *et al.* 1985*a*). Since unit B was maintained at 10 impulses s^{-1}, this is equivalent to the extra event unit A discharges linked to unit B discharges per 100 ms.

RESULTS

Spinal lesions and first dorsal interosseous muscle motor unit synchronization

Figure 1 shows three PPSTHs obtained from first dorsal interosseous motor units during weak voluntary isometric abductions of the index finger of the right hand in three separate subjects. The top panel of Fig. 1 shows a PPSTH obtained in a normal subject. The histogram is dominated by a single peak of duration 12·1 ms around time zero. The middle panel of Fig. 1 shows a PPSTH obtained in a patient with a cerebrovascular accident (T. T., see Table 1; infarction of the contralateral cerebral hemisphere). The peak in the histogram is much broader (47·9 ms) and the short-term synchronization is almost absent. The lower panel of Fig. 1 shows a PPSTH obtained in a patient with malignant infiltration of his cervical spinal cord from prostatic carcinoma. Again, in contradistinction to the histogram obtained in the normal subject, the histogram is dominated by a peak of broad duration with short-term synchronization being almost absent. In another patient with a spinal abscess and antibioma excised at T9, i.e. caudal to the first dorsal interosseous motoneurone pool, normal short-term synchronization was seen. This suggests that the cervical spinal cord above the motoneurone pool and the contralateral cerebral cortex must be intact for the generation of short-term synchronization and furthermore this suggests that established lesions of the contralateral cerebral cortex and spinal cord rostral to the motoneurone pool lead to the production of broad duration synchronization.

The strength of synchronization (e/T), expressed as the extra (synchronized) unit A spikes in the peak of the PPSTH greater than control (e) as a proportion of the total number of reference (stimulus) unit spikes (T), is given by the height of the cusum between points of inflexion as a proportion of the number of sweeps used to compute the PPSTH. In Fig. 1, the overall strength of synchronization in the broad duration central peaks of the PPSTHs from the two patients is greater than that seen in the short-term central peak of the PPSTH from the normal subject.

Radiological confirmation of the lesions in the patients shown in Fig. 1 are shown in Fig. 2. Figure 2*A* shows the computerized axial tomography (CAT) scan of the brain of the patient T. T. with the cerebrovascular accident whose PPSTH is shown in the middle panel of Fig. 1. A large area of decreased density of the left cerebral hemisphere is shown, compatible with an infarction of the left parietal lobe. Figure 2*B* shows CAT scans at the level of C7–T2 of the patient whose PPSTH histogram is shown in the bottom panel of Fig. 1. It shows extensive spinal destruction with cord compression. Figure 2*C* shows the cervical myelogram from the same patient whose cervical CAT scans are shown. There is a complete block to the passage of dye rostral to T1.

Figure 3*A* displays the group results for duration of synchronization of motor units in first dorsal interosseous muscle from eighteen normal subjects and the seven patients who had suffered strokes. The mean duration of synchronization is significantly greater in the stroke patients than in the normal subjects ($P < 0{\cdot}001$;

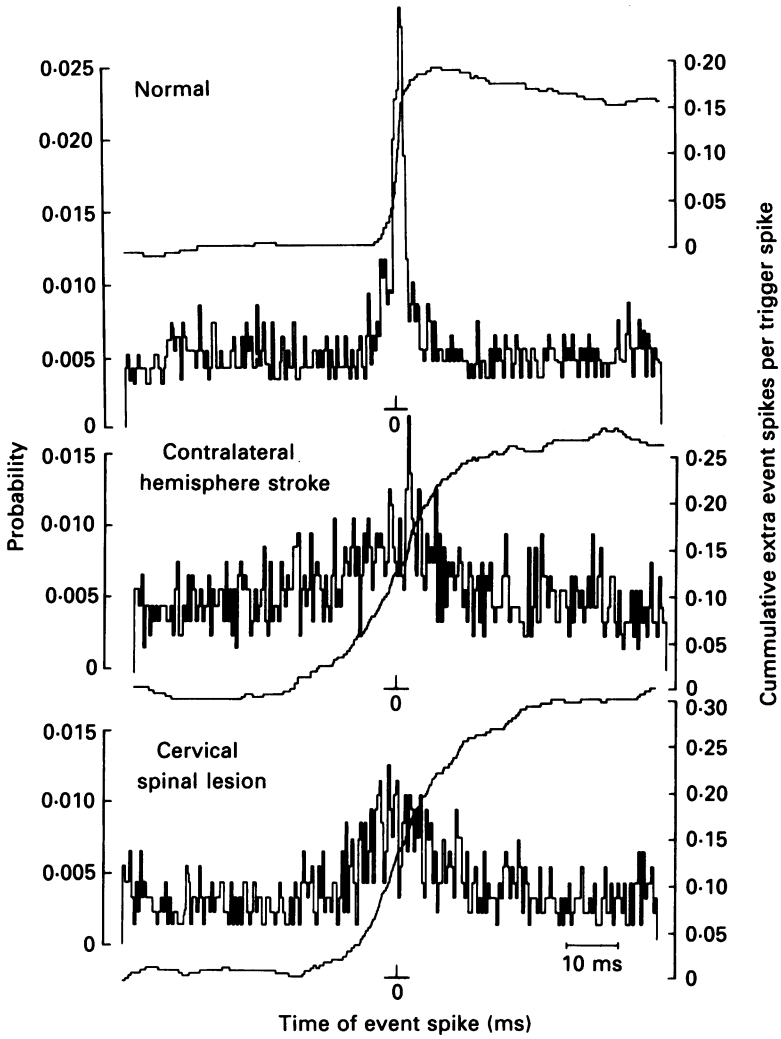

Fig. 1. Synchronization of motor unit firing in 1DI. PPSTHs (bin width 391 μs; 1000 sweeps (reference stimulus unit B spikes) and corresponding cusums of motor unit firing recorded during weak steady voluntary isometric abduction of the right index finger. In all three panels, unit B is maintained at a steady discharge rate of 10 impulses s^{-1}. The top panel is from a normal subject, the middle panel from a patient with a contralateral cerebral hemisphere infarction (T. T., see Table 1) and the lower panel from a patient with a C7–T1 partial spinal lesion. Strength of synchronization is given by the height of the cusum between inflexions for the duration of synchronization and was 0·184, 0·250 and 0·2292 extra event unit spikes per reference unit B spikes for the top, middle and lower panels respectively.

unpaired t test). Figure 3B shows the group results for strength of synchronization for the data shown in Fig. 3A. The mean strength of synchronization is significantly greater in the stroke patients than in the normal subjects (see Table 2; $P < 0{\cdot}001$, unpaired t test of pooled data; $P = 0{\cdot}05$, unpaired t test of subjects' median results). In the patient with the rostral cervical spinal lesion, the duration of synchronization

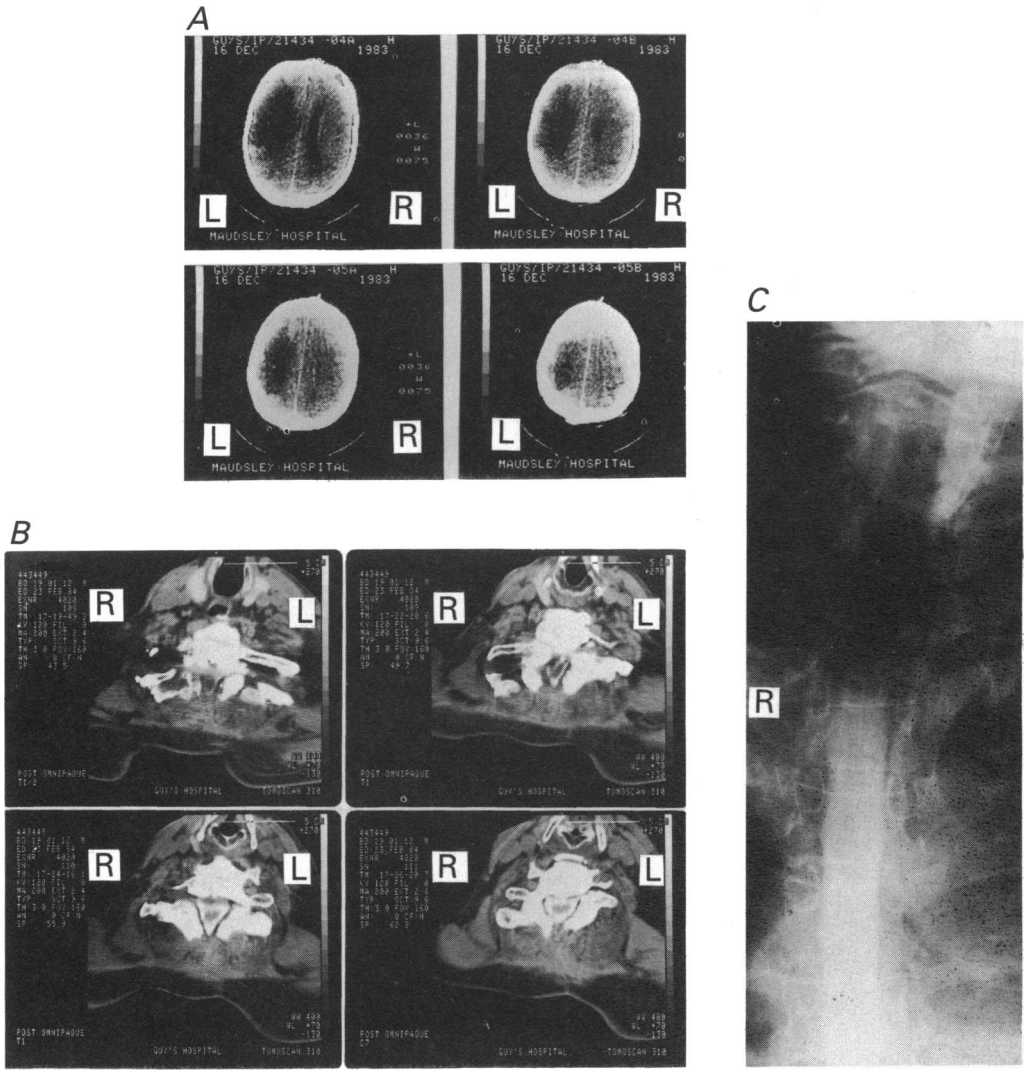

Fig. 2. Radiological identification of central nervous lesions. *A* shows a CAT scan of the brain of the stroke patient (T. T., see Table 1) whose PPSTH is shown in the middle panel of Fig. 1. *B* and *C* show the cervical spine CAT scan and cervical myelogram of the patient with malignant spinal infiltration whose PPSTH is shown in the bottom panel of Fig. 1.

was 43–46 ms ($n = 2$) whereas in the patient with the caudal T9 spinal lesion the duration of synchronization was 20·7–22·4 ms ($n = 2$). The strength of synchronization was greater in both pairs of motor units studied in the patient with the rostral cervical lesion (0·26, 0·54 extra event unit spikes per reference unit B spike) than in the patient with the caudal T9 lesion who had values in the normal range (0·078, 0·131 extra event unit spikes per reference unit spike).

Stroke and lower limb muscle motor unit synchronization

The synchronization of motor unit discharge in medial gastrocnemius (MG) in two normal subjects and a stroke patient is shown in Fig. 4. The strength of synchronization in normal subjects is weak for MG motor units and by comparison

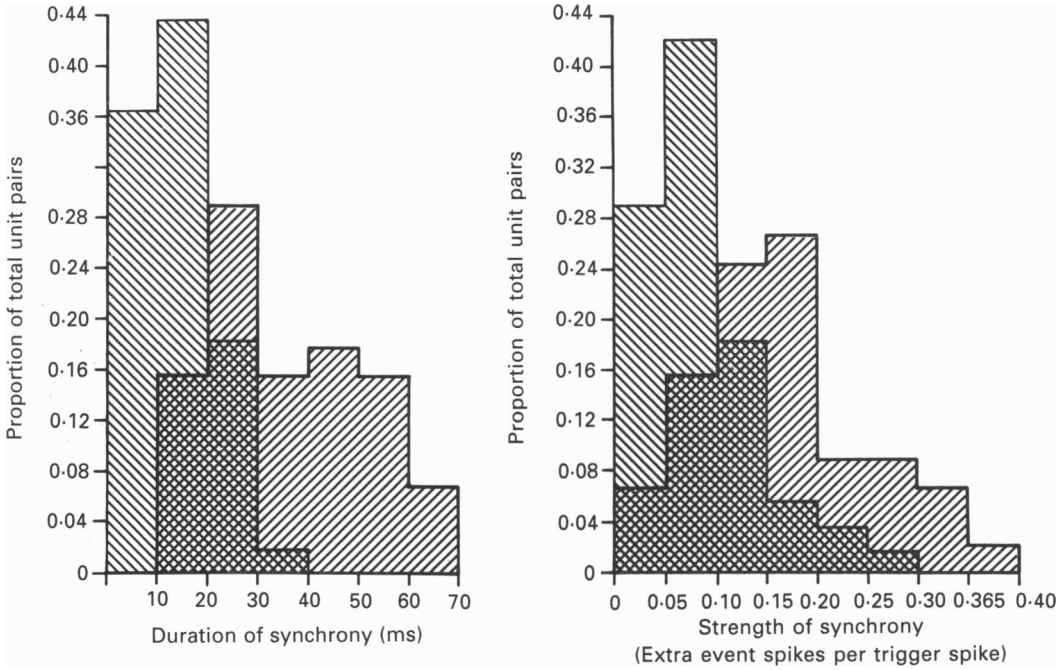

Fig. 3. Group results for duration (*A*) and strength (*B*) of synchronization in eighteen normal (▧) and seven patients with stroke affecting the limb (▨) were studied. The mean strength and duration of synchronization was significantly greater in the stroke patients than in the normal subjects ($P < 0{\cdot}001$; unpaired t test). Normal patients, $n = 55$; stroke patients, $n = 45$ (n = motor unit pairs).

with the example in the top panel of Fig. 1 is less than that for first dorsal interosseous muscle (1DI). Following a stroke the synchronization strength for MG motor units on the affected limb increases, but it is still less than that seen in 1DI either in the normal subject or in the stroke patients.

Figure 5 shows examples of PPSTHs of the firing of motor units in tibialis anterior (TA) in two normal subjects and a stroke patient. In normal subjects the strength of synchronization between the discharges of TA motor units was less than that seen between the discharge of motor units in 1DI, but was usually greater than that seen in MG (see Fig. 4). Figure 5 also shows that there does not appear to be a difference in the strength of synchronization of TA motor units in the affected limb of a stroke patient compared to that seen in the two normal subjects shown.

The group results for strength of synchronization of MG motor units in five normal subjects and six stroke patients and of TA motor units in four normal subjects and five stroke patients are displayed in Fig. 6. This shows that for both MG and TA

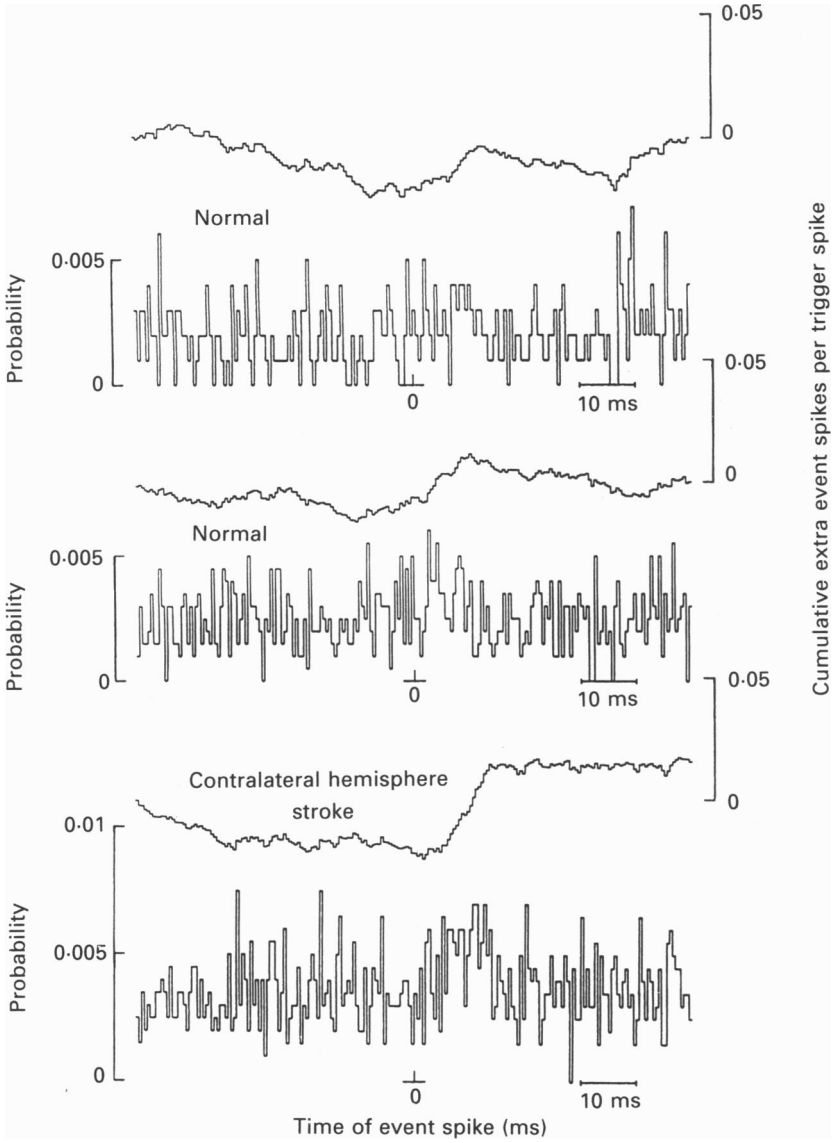

Fig. 4. Synchronization of motor unit firing in MG. PPSTHs (bin width 500 μs; top panel 1000 sweeps (reference unit B spikes); lower panels 2000 sweeps) and corresponding cusums of motor unit firing during weak steady voluntary isometric dorsiflexion of the ankle. In all three panels, unit B is maintained at 10 impulses s^{-1}. The top panels are histograms obtained for two normal subjects. The PPSTH in the lower panel was computed from a pair of MG motor units in the affected limb of a patient with an infarction of the contralateral cerebral hemisphere. The strength of synchronization was 0·012 and 0·029 extra event spikes per reference event B spike for the upper panels (normal subjects) and 0·038 extra event unit spikes per reference unit B spike for the bottom panel (stroke patient).

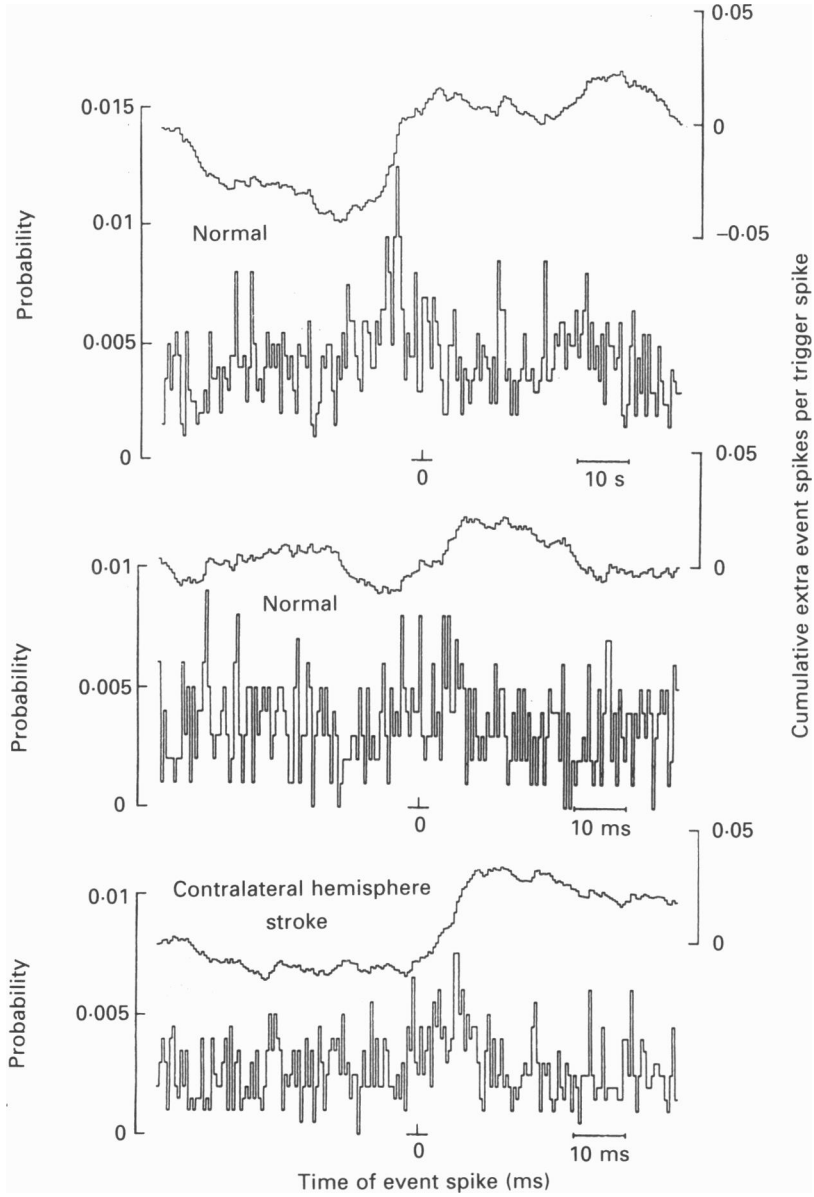

Fig. 5. Synchronization of motor unit firing in TA. PPSTHs (bin width 500 μs; top and bottom panel 2000 sweeps (reference unit B spikes), middle panel 1000 sweeps) and corresponding cusums of motor unit firing during weak and steady voluntary isometric plantarflexion of the ankle. In all three panels unit B is maintained at 10 impulses s^{-1}. The top two panels are histograms obtained from two normal subjects. The PPSTH in the bottom panel was computed from TA motor units in the affected limb of a patient with infarction of the contralateral cerebral hemisphere. The strength of synchronization was 0·060 and 0·033 extra event unit spikes per reference unit B spike for the top and middle panels (normal subject) and 0·043 extra event unit spikes per reference unit B spikes for the bottom panel (stroke patient).

motor units, following a stroke there is a proportion (20%) of motor unit pairs that show greater than normal strength of synchronization. These data are compared with the data for 1DI motor units in eighteen normal subjects and seven stroke patients in Table 2. The strength of synchronization in normal subjects is greater in

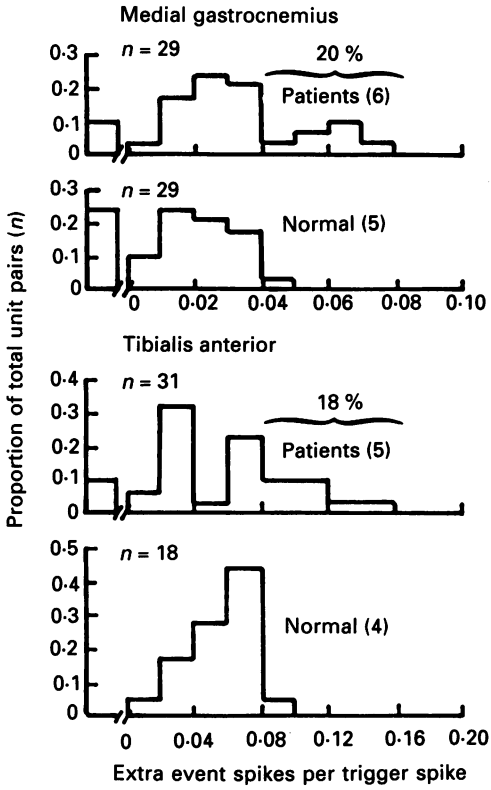

Fig. 6. Group results for strength of synchronization of motor unit firing in MG (five normal subjects and six patients with stroke affecting the limb studied) and TA (four normal subjects and five stroke patients). For MG, 20% of the data in the stroke patients, but only 3% in the normal subjects was greater than 0·04 extra event unit spikes per reference unit spike. For TA, 18% of the data in the stroke patients but only 6% of the data in normal subjects was greater than 0·08 extra event spikes per reference unit spike.

motor units of 1DI than it is in TA ($P < 0{\cdot}005$; unpaired t test) and greater in TA than it is in MG ($P < 0{\cdot}001$; unpaired t test). In normal subjects synchronization was present in every 1DI and TA motor unit pair but was not discernable in five of twenty-nine pairs of MG motor units. The clinical details of the stroke patients are given in Table 1.

It may be seen from Table 2 that following a stroke, motor units on the affected side in 1DI and MG showed greater synchronization than in normal subjects but only significantly so for MG when pooled data was compared. The mean strength of

TABLE 2. Synchronization of motor unit firing in normal subjects and in motor units on the affected side of stroke patients

	Strength of synchronization (extra event spikes per reference unit spike)			Duration of synchronization (ms)		
	1DI	MG	TA	1DI	MG	TA
			Normal subjects			
Range	0·042–0·280	0–0·043	0·016–0·079	4·0–28·0	3·5–21·7	3·0–25·0
Mean ± S.D.	0·086 ± 0·054	0·016 ± 0·013	0·056 ± 0·022	13·9 ± 6·7	10·3 ± 4·4	13·5 ± 6·1
Motor unit pairs	55	29	18	55	22	18
Subjects (range of unit pairs per subject)	18 (2–12)	5 (4–8)	4 (1–7)	18 (2–12)	5 (4–8)	4 (1–7)
Mean ± S.D. of subjects' median results	0·082 ± 0·052	0·020 ± 0·010	0·050 ± 0·023	10·6 ± 8·6	9·7 ± 0·9	12·4 ± 4·5
			Stroke patients			
Range	0·017–0·391	0–0·072	0–0·141	12·0 ± 65·0	4·0 ± 43·0	14·0 ± 49·0
Mean ± S.D.	0·161 ± 0·089	0·30 ± 0·020	0·055 ± 0·039	35·4 ± 14·8	21·3 ± 10·8	28·8 ± 11·3
Motor unit pairs	45	29	31	45	26	28
Subjects (range of unit pairs per subject)	7 (3–11)	6 (1–7)	5 (2–7)	7 (3–11)	6 (1–7)	5 (2–7)
Mean ± S.D. of subjects' median results	0·159 ± 0·081	0·036 ± 0·023	0·043 ± 0·027	35·6 ± 13·9	20·5 ± 8·6	26·7 ± 6·6
P_1 (normal *vs.* stroke)	< 0·001	< 0·01	> 0·1	< 0·001	< 0·001	< 0·001
P_2 (normal *vs.* stroke)	0·05	0·19	0·69	0·002	0·03	0·006

P_1 (normal *vs.* stroke) refers to the probability of the null hypothesis in an unpaired t test between the grand means for each group; n used in test being the number of unit pairs. P_2 (normal *vs.* stroke) refers to the probability of the null hypothesis in an unpaired t test between the means of each subject's median result in the two groups; n used in test being the number of subjects.

synchronization between the discharge of TA motor units was, however, similar in stroke patients and normal subjects. Nevertheless, following a stroke the rank order of strength of synchronization of motor unit firing in 1DI, MG and TA is the same as in the normal subjects; the strength in 1DI was significantly greater than that

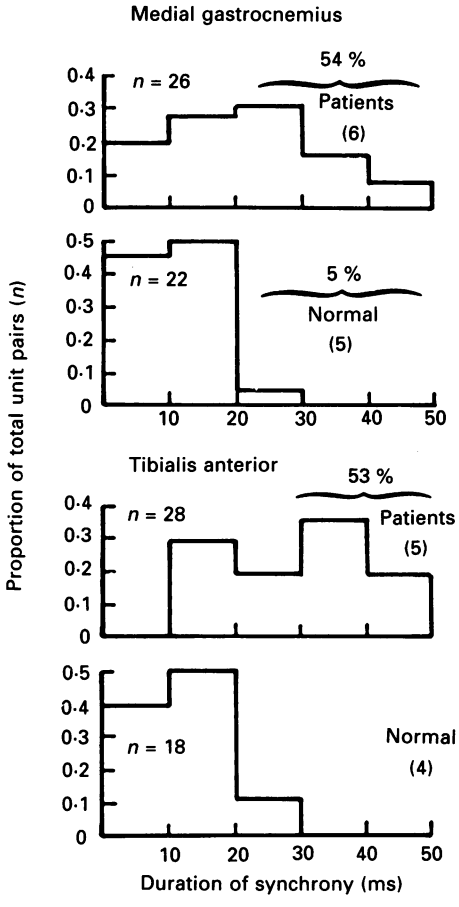

Fig. 7. Group results for duration of synchronization of motor unit firing in MG and TA. The subjects studied are the same as those whose results are displayed in Fig. 6. For MG, 54 % of the data in the stroke patients but only 5 % in the normal subjects was greater than 25 ms in duration. For TA, 53 % of the data in the stroke patients and none of the data in the normal subjects was of duration greater than 30 ms.

seen in TA ($P < 0{\cdot}001$; unpaired t test) and greater in TA than in MG ($P < 0{\cdot}01$; unpaired t test).

For the subjects whose data is displayed in Fig. 6, the group results for duration of synchronization of MG and TA motor units are shown in Fig. 7 and compared with those for 1DI motor units in Table 2. In normal subjects, the duration of synchronization is comparable in all three muscles. Following a stroke, the duration is significantly greater for motor units of 1DI, MG and TA on the affected side than it is in the corresponding muscle in a normal subject. There was a significantly longer

duration of synchronization in 1DI motor units than in TA or MG ($P < 0.05$ and $P < 0.01$ respectively; unpaired t test) and in TA than in MG ($P < 0.01$; unpaired t test). In the two spinal patients, short-term synchronization was only seen in one pair of motor units in MG and never between any pair of TA motor units and was replaced by broad duration synchronization (mean duration of synchronization for MG 18 ms,

TABLE 3. Synchronization of 1DI motor unit discharge in patients with basal ganglia and cerebellar lesions

		Strength of synchronization (extra event unit spike per reference unit spike)		Duration of synchronization (ms)	
CNS pathology	n	Mean	Range	Mean	Range
Untreated Parkinson's disease	4	0·250	0·204–0·278	41·0	37–45
Huntington's chorea	2	0·151	0·128–0·174	14·5	9–20
Cerebellar haematoma	2	0·153	0·130–0·175	23·5	19–28

n refers to the number of motor unit pairs studied.

range 10–24 ms, $n = 5$; mean duration of synchronization for TA 33·6 ms, range 24–52 ms, $n = 5$).

Basal ganglia and cerebellar lesions

The synchronization of motor unit discharge in the right 1DI of a patient with untreated, newly diagnosed Parkinson's disease, a patient with Huntington's chorea and a patient with a bilateral cerebellar haematoma is summarized in Table 3. Short-term synchronization was seen in the patient with Huntington's chorea; the duration and strength of synchronization are normal. Short-term synchronization was absent in the patient with the cerebellar lesion. It was replaced by broad duration synchronization; the strength of synchronization however is normal. The mean duration and strength of synchronization in Parkinsons's disease is found to be on the upper limits of the normal range, with individual observations for both duration and strength outside of the normal range. Short-term synchronization was not seen in any of the four pairs of motor units studied in this patient.

Synchronization between antagonist and adjacent muscles in normal subjects

The distribution of synchronization of motor unit firing between different motoneurone pools was studied by constructing a PPSTH of the discharge of event motor unit A in one muscle, before and after the discharge of a reference motor unit B in another muscle. Figure 8 shows examples between motor units in antagonist muscles: in the top panel, a subject is required to use his index finger to point by extension of the metacarpophalangeal and interphalangeal joints. Recordings are made from a 1DI unit (index finger abductor) and from a unit in second palmar interosseous muscle (2PI; index finger abductor). In the lower panel a subject is quietly standing and recordings are made from a motor unit in the ankle extensor,

MG and a motor unit in the ankle flexor, TA. In both cases synchronization of motor unit firing is seen; however it is weaker than that seen between motor units in the homonymous muscle. Synchronization was seen between every pair of 1DI–2PI ($n = 4$) and MG–TA ($n = 9$). In a companion paper (Bremner, Baker & Stephens,

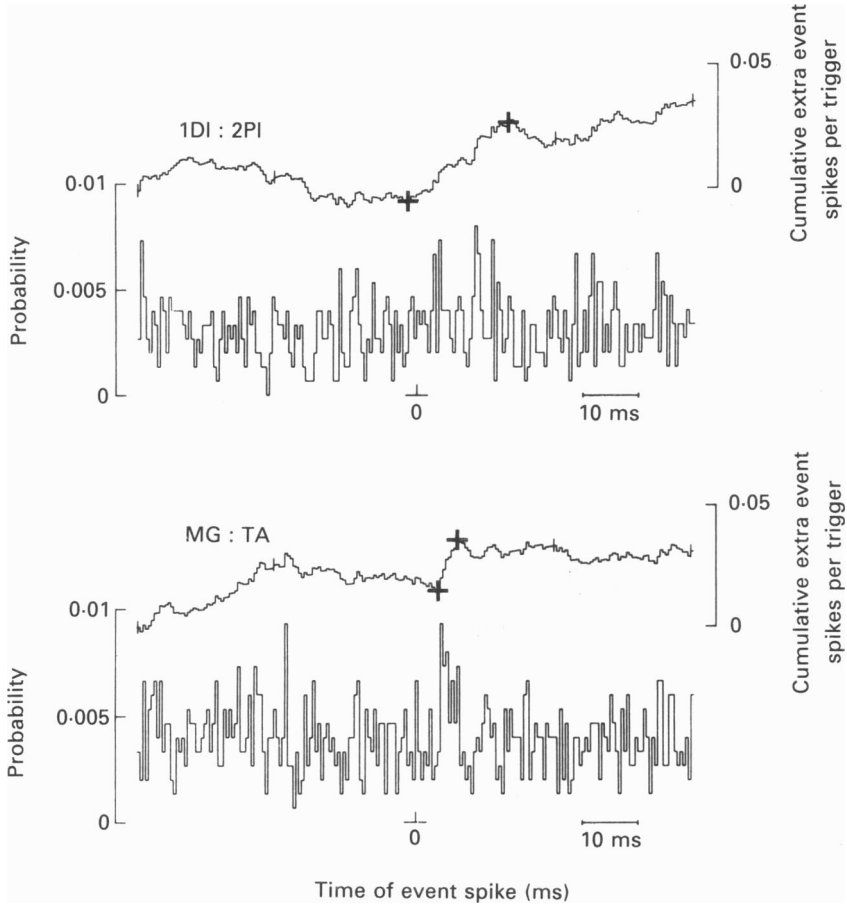

Fig. 8. Synchronization of motor unit firing in antagonist muscles of normal subjects. PPSTHs (bin width 500 μs, 1500 sweeps (reference unit B spikes) and corresponding cusums above). In the upper panel a reference unit B in the index finger abductor 1DI is maintained at a steady firing rate of 10 impulses s^{-1} and is correlated with an event unit in the second palmar interosseous (2PI). In the lower panel, a reference unit B in the ankle extensor MG is correlated with an event unit in TA. The duration of synchronization is given by the period between inflexions of the cusum, marked with crosses. Duration of synchronization 16·5 and 4·0 ms for 1DI:2PI and MG and TA respectively. Strength of synchronization was 0·029 and 0·022 extra event unit spikes per reference unit B spike for 1DI:2PI and MG:TA respectively.

1991*a*) synchronization between 1DI/2PI during a different task (index finger flexion) is discussed.

Figure 9 shows that the strength of synchronization was greater in a normal subject between motor units of muscles that were closer anatomically than between

motor units of muscles that were further apart. The top panel of Fig. 9 shows clear synchronization between a reference 1DI motor unit (index finger abductor) paired with a unit in the middle finger abductor, second dorsal interosseous muscle (2DI). The lower panel of Fig. 9 shows that there is less synchronization between the same

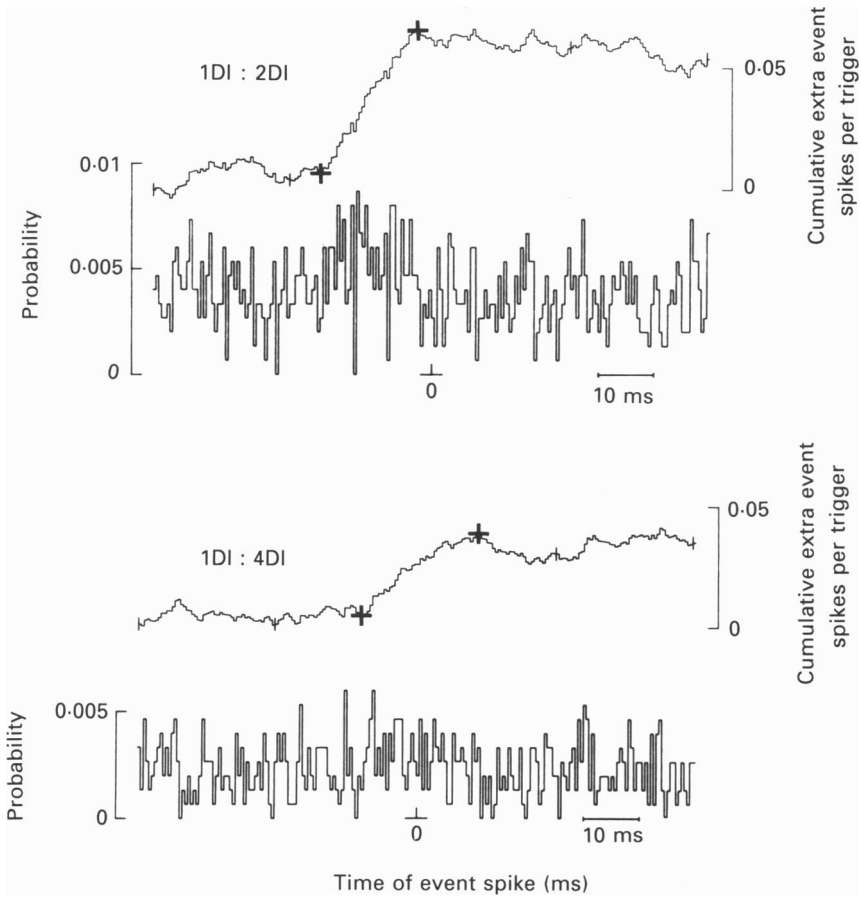

Fig. 9. Synchronization of motor unit firing between intrinsic hand muscles in a normal subject. PPSTH (bin width 500 μs; 1500 sweeps (reference unit B spikes)) and corresponding cusum between the firing of a reference unit B in 1DI correlated with an event unit in second dorsal interosseous muscle (2DI) in the upper panel. The lower panel shows the PPSTH and cusum of the firing of the same reference 1DI unit and a motor unit in fourth dorsal interosseous muscle (4DI). The 1DI unit was maintained at 10 impulses s^{-1} in both cases. Strength of synchronization calculated, as shown in Fig. 8, was 0·053 and 0·031 extra event unit spikes per reference 1DI unit B spike for 1DI:2DI and 1DI:4DI respectively. The duration of synchronization is given by the period between inflexions of the cusum, marked with crosses.

1DI reference unit and a unit in the ring finger abductor, fourth dorsal interosseous muscle (4DI). The same result was obtained in three separate experiments (two subjects).

Synchronization between adjacent muscles in stroke

In their study of the effect of spinal cord hemisection on intercostal motoneurone synchronization in the cat, Kirkwood *et al.* (1984) reported that the strength of broad-peak synchronization was much less dependent on segmental separation than

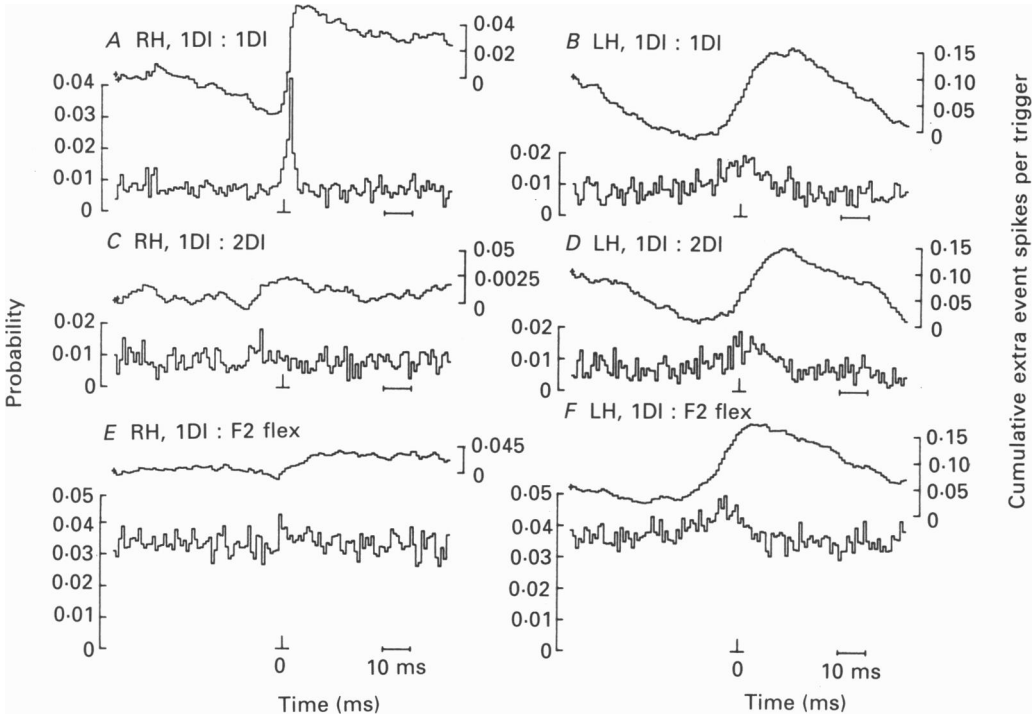

Fig. 10. The spread of broad-peak synchronization. Cross-correlograms constructed of the firing of motor units recorded from different muscles on the unaffected and affected sides of a patient with a right cerebral infarction. *A*, *C* and *E*, unaffected side, right hand (RH). *B*, *D* and *F*, affected side, left hand (LH). *A*, RH 1DI : 1DI (1803); *B*, LH 1DI : 1DI (1771); *C*, RH 1DI : 2DI (1305); *D*, LH 1DI : 2DI (1265); *E*, multiunit record RH 1DI : index finger portion of flexor digitorum superficialis (F2 flex) (3972); *F*, multiunit record LH 1DI : F2 flex (4146); figures in parentheses refer to number of reference unit spikes used to construct cross-correlogram. Strength of synchronization expressed as extra event spikes per reference unit spike for *A*–*F*; 0·084, 0·165, 0·027, 0·138, 0·052 and 0·166 respectively. Bin width 1 ms.

was the strength of short-term synchronization. We have found a similar result in the present study. An example in a patient with an infarction of the right cerebral cortex is shown in Fig. 10. Figure 10*A* and *C* shows cross-correlograms constructed between the firing of two motor units within 1DI (*A*) and between units in 1DI and 2DI (*C*) on the unaffected side. The synchronization is of short duration and decreases in a fashion similar to that found by Bremner, Baker & Stephens (1991*b*). For comparison Fig. 10*B* and *D* shows in the same patient cross-correlograms constructed between

the firing of units within 1DI (*B*) and between 1DI and 2DI (*D*) on the affected side. In this case the synchronization is of broad duration in both muscle combinations and of similar strength within 1DI as between 1DI and 2DI. Figure 10*E* and *F* shows cross-correlograms constructed between multiunit EMG recorded from 1DI and the

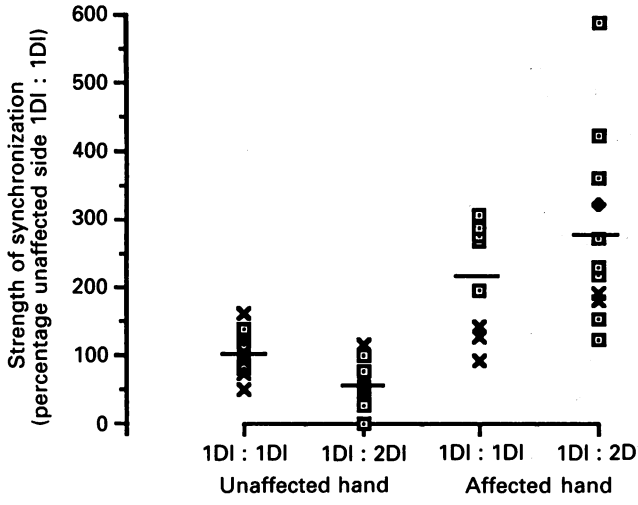

Fig. 11. Distribution of synchronization within and between intrinsic hand muscle motoneurone pools in stroke. Strength of synchronization normalized for each patient to the median value obtained in that patient for units within 1DI on the unaffected side. Mean of medians for the three patients for each condition shown by horizontal lines. Results for each patient given by different symbols.

index finger portion of flexor digitorum superficialis on the unaffected (*E*) and affected side (*F*). The synchronization seen in Fig. 10*E* is of short duration and weak, whereas the synchronization seen in (*F*) is of broad duration and strong. The broad-peak synchronization seen in Fig. 10*B*, *D* and *F* is therefore widely distributed and equally strong between motor nuclei as it is within the same motor nucleus. The same result was obtained in two further patients with strokes; data from the three patients are shown graphically in Fig. 11 which compares the strength of synchronization between units in 1DI and 2DI and within 1DI on the affected and unaffected side. On the affected side values for strength of synchronization are greater than on the unaffected side for units between 1DI and 2DI as well as within 1DI. On the unaffected side the strength of synchronization between units in 1DI and 2DI appears to be less than that seen for units within 1DI, consistent with the findings in normal subjects studied by Bremner *et al.* (1991*b*). In contrast the range of values on the affected side for units between 1DI and 2DI encompasses the range of values for units within 1DI. The lack of any clear gradient of broad-peak synchronization and its wide distribution between motoneurone pools on the affected side in patients with stroke suggests that the broad-peak synchronization observed in these patients behaves in a similar manner to that observed for intercostal motoneurones of cats with acute (Kirkwood *et al.* 1982*a*; Kirkwood, Sears, Tuck & Westgaard, 1982*b*) and established (Kirkwood *et al.* 1984) rostral spinal lesions.

DISCUSSION

Mammalian motor units do not fire independently but have a tendency to fire together. In the present study, PPSTHs of the time of discharge of one motor unit relative to the time of discharge of another demonstrate a narrow central peak, termed short-term synchronization, in all muscles studied of normal subjects. It was not always observed between all motor unit pairs in the larger limb muscles. It can also be observed between the firing of a reference unit in one muscle and units in both adjacent and antagonist msucles.

Sears & Stagg (1976) put forward the hypothesis that the joint occurrence of unitary EPSPs evoked in motoneurones by branches of common stem presynaptic neurones produced synchronization of their discharges. Subsequently Kirkwood & Sears (1978) obtained support for this hypothesis by showing that equations developed from an explicit model of the branched stem hypothesis fitted the time course of synchronization of cat intercostal motoneurone firing and its intracellular equivalent, the average common excitation potential. We have used the same equations to examine the time course of synchronization of human intrinsic hand muscle and forearm muscle motor unit firing and found that the theoretical time course of synchronization matches all of the observed results (Datta & Stephens, 1983, 1990; Bremner *et al.* 1991*a*). Short-term synchronization in human muscles is therefore analogous to that seen in cat intercostal muscles and in both cases can be attributed to the joint occurrence at the motoneurone of EPSPs derived from the branches of common presynaptic stem fibres.

The importance of this theoretical background for the understanding of short-term synchronization of motor unit discharge is that it allows the presence of synchronization between the firing of motoneurones to be used as an indication of the presence of shared input and hence infers features of the organization and activity of common, branched-stem presynaptic fibres between and within motoneurone pools. The results of the present study indicate that these common branched-stem presynaptic fibres are active within and between all motoneurone pools, but are most active within the homologous motoneurone pool and least active between motoneurone pools of muscles that are widely separated. A quantitative analysis of this for the finger muscles is given in a companion paper (Bremner *et al.* 1991*b*). These results are consistent with those of Kirkwood *et al.* (1982*a*). They found that short-term synchronization of cat intercostal motoneurones was stronger between adjacent thoracic segments than between more widely separated thoracic segments.

In this study comparison of the results within different homologous motoneurone pools suggest that these common branched-stem presynaptic axons are relatively more active in intrinsic hand muscles and less active in large limb muscles. This observation is incompatible with a hypothesis of the peripheral afferent origin of the common branched-stem presynaptic axons: individual muscle spindle primary afferents are capable of monosynaptically innervating almost all of the homologous triceps surae motoneurone pool (Harrison & Taylor, 1981). On that basis we might expect activity of muscle spindle afferents to be involved in the generation of short-term synchronization. However, in contrast to its easy elicitation in triceps surae, the stretch reflex is not present in intrinsic hand muscles of normal subjects. In

other words, the distribution of short-term synchronization we have seen in the present study is not consistent with the distribution of peripheral afferent input. Furthermore, in the cat, short-term synchronization of the intercostal motoneurone discharge is unaffected by dorsal root section (Kirkwood *et al.* 1982*b*) and in triceps surae motoneurones is only minimally reduced (Powers & Rymer, 1988). Similarly, in a man with a post-infective large-fibre sensory neuropathy, short-term synchronization was also claimed to be normal (Baker, Bremner, Cole & Stephens, 1988). It should also be remembered that only 0·5% of synaptic boutons on cat lumbosacral motoneurones are monosynaptic contacts from dorsal root fibres (Conradi, 1969). Taken together these results suggest a central rather than peripheral origin for the presynaptic neurones producing short-term synchronization of motoneurone discharge.

In contrast to peripheral afferents the pyramidal tract is known to monosynaptically activate intrinsic hand muscles powerfully (Clough, Kernell & Phillips, 1968); futhermore, individual corticospinal axons branch to supply many motoneurone pools (Asanuma, Zarzecki, Jankowska, Hongo & Marcus, 1979; Shinoda, Zarzecki & Asanuma, 1979). Indeed, 100 years ago Sherrington (1889) showed that small lesions of the motor cortex resulted in degeneration of fibres at all levels of the spinal cord. Lastly, the extensive motor fields of pyramidal tract neurones known to be active and to innervate motoneurones in muscles active during a voluntary contraction are known (Fetz & Cheney, 1978). Persuasive as these arguments appear, observations on the distribution of strength of synchronization within and between different motoneurone pools in normal subjects are insufficient in themselves to establish the central cortical origin of the common branched-stem presynaptic pathways underlying short-term synchronization. Additional, complementary evidence is provided by the results from patients with established, well-identified neurological lesions.

Spinal lesions and synchronization

The marked reduction in short-term synchronization between the firing of human motor units caudal but not rostral to a partial spinal lesion seen in the present study suggests that activity of neurones or fibres within the rostral spinal cord is required to generate the common branched-stem presynaptic activity necessary for short-term synchronization during voluntary contractions. This finding is analogous to that seen in the anaesthetized cat caudal and ipsilateral to an acute or established hemisection of the spinal cord where short-term synchronization of intercostal motoneurone activity is usually abolished (Kirkwood *et al.* 1982*b*, 1984). In that study, and in the present study, motoneurone synchronization is of the broad-duration type. This has been attributed to presynaptic synchronization (Kirkwood *et al.* 1982*b*) which probably comes from spinal neurones from a heterogenous group of systems, including propriospinal (Kirkwood *et al.* 1984). Anatomical evidence that propriospinal neurones may play a part in the production of presynaptic synchronization comes from the work of Pullen & Sears (1978). Those authors show that in the same animals studied by Kirkwood *et al.* (1984), 'C' synapses, which are thought to derive from spinal intrasegmental propriospinal neurone pathways, increased in frequency caudal to the hemisection over a period of 6 months and showed a territorial extension onto dendrites not normally exhibiting 'C'-type

synapses. In a later study (Pullen & Sears, 1983) they suggested that this was part of a compensatory response to partial central deafferentation. Nevertheless, it should be remembered that the time course of the physiological changes in motoneurone behaviour (Kirkwood *et al.* 1984) is much faster than that of the anatomical changes in the same animals (Pullen & Sears, 1978). It is possible that synchronization of other residual central presynaptic neurones occurs.

Cortical lesions and synchronization

Following a cortical stroke motor units of muscles on the affected side also show a marked reduction or abolition in short-term synchronization to be replaced by broad-duration synchronization. This result strongly suggests that descending cortical pathways with branched-stem axons are instrumental in the generation of the powerful short-term synchronization seen during voluntary contractions. An alternative hypothesis is that cortical excitation of branched-stem spinal interneurones presynaptic to motoneurones occurs. Thus, we would conclude that corticospinal pathways during human voluntary contractions are analogous to bulbospinal pathways during respiration in the cat, which have been argued as being necessary for the generation of short-term synchronization, either directly or indirectly via spinal interneurones (Kirkwood *et al.* 1982*a*; Davies, Kirkwood & Sears, 1985). We cannot be certain of the mechanism of generation either of broad-term synchronization or of the spasticity and hyperreflexia in the stroke patients, but the most parsimonious explanation is that it is the same as that which occurs caudal to a spinal lesion.

The results of the present study show that following a cortical stroke the strength of synchronization increased in motor units of 1DI and the limb extensor MG, but not TA. The validity of this result depends on the sample of motor units being analysed in the stroke patients as being equivalent to those analysed in the normal subjects, since the strength of synchronization is markedly dependent on the relative recruitment thresholds of the units studied, being greatest for those of similar recruitment threshold and least for those of widely varying threshold (Datta & Stephens, 1980, 1990; Datta, Fleming, Hortobagyi & Stephens, 1985*d*). This is particularly important since following partial central deafferentation by acute dorsal spinal hemisection in the decerebrate cat, a compression of the range of motoneurone recruitment threshold forces, with some reversal of recruitment occurring, was observed by Powers & Rymer (1988). While we have not analysed this problem in our subjects, we have taken particular care to record from units active during the weakest possible contraction in both normal subjects and the patients. It could also be argued that the normal subjects are not adequate controls because, for example, they are of different ages. However, this is overcome by the observations in the three stroke patients where normal short-term synchronization is seen in the unaffected limb, and strong broad-duration synchronization on the affected side (see Figs 10 and 11).

The increase in synchronization of broad duration in lower limb extensor rather than flexor muscles suggests increased synchronized activity of interneurones projecting to extensor rather than flexor motoneurone pools. This differential effect on the different interneurone populations may also underlie the common clinical finding of increased muscle tone and hyperreflexia of leg extensor rather than flexor

muscles in these patients. This hypothesis could be tested directly by examining the increase in broad-duration synchronization in motor units of the upper limb musculature, where increased tone and hyperreflexia is seen more on the flexor rather than extensor muscles.

Internal capsule lesions and first dorsal interosseous muscle motor unit synchronization

In their study of eight stroke patients Bremner, Farmer, Farmer, Ingram, Stephens & Swash (1989) found synchronization within 1DI motor units on the affected side which was of shorter duration (mean 18 ms, S.D. 10 ms) than that found in the present study and were able to model the correlograms using Kirkwood's equations of the branched presynaptic axon hypothesis (Kirkwood & Sears, 1978). In contrast to the patients of the present study who had strokes predominantly (6/7) due to cortical infarctions and were hypertonic, the patients studied by Bremner *et al.* (1989) had strokes which were predominantly (7/8) due to lacunar infarctions of the internal capsule and displayed normal tone on the affected side. Thus there may exist a relationship between anatomical site of lesion, motor deficit and type of motor unit synchronization.

Basal ganglia and cerebellar lesions

Broad-duration synchronization of increased strength and diminished short-term synchronization was seen in the patient with untreated Parkinson's disease. The results are consistent with those of Dengler, Wolf, Schubert & Struppler (1986) who also found broad-duration synchronization in 1DI motor units of seven patients with Parkinson's disease, two of which did not have any clinically manifest tremor. Those authors did not comment on the treatment status of their patients. On the basis of the data from the present study combined with that from Dengler *et al.* (1986) we would speculate that extra pyramidal pathways may also be necessary for the generation of short-term synchronization during voluntary contractions and that basal ganglia lesions may also lead to the increased synchronized activity of spinal interneurones or other central neurones projecting to the motoneurones studied. It should be noted that Davey, Ellaway & Friedland (1986) found broad, oscillating peaks in cross-correlograms of more proximal limb muscles (TA and extensor digitorum communis) in patients with Parkinson's disease, whose treatment status was not stated. They claimed that the oscillations in those patients were most marked when the patients exhibited strong tremor. They also suggested that overall there may be a higher incidence of tight synchronization (defined as half-width of histogram peak $< 12{\cdot}5$ ms) in those muscles in the Parkinson's disease patients than in normal subjects. Thus it is not possible to compare our results with those of Davey *et al.* (1986) directly. Nevertheless, further work examining synchronization in different muscles of these patients would be valuable particularly pre- and post-treatment and with quantitative correlation with motor dysfunction (e.g. tremor).

The absence of short-term synchronization and its replacement by broad-term synchronization in the 1DI motor units of the patients with the cerebellar lesion is predictable, given the same results in the patients with cortical strokes and the known cerebro-cerebellar interactions. For example, the cerebellum and motor

cortex are major inputs to the magnocellular red nucleus, whose output in primates is to the contralateral spinal cord, terminating at similar sites to that of the corticospinal tract among interneurones and laterally placed motor neurones which innervate distal muscles (Kuypers, Fleming & Farinholt, 1962). Similarly, cerebellar dentate and interpositus nuclei project strongly onto motor cortical cells with marked spatial facilitation (Shinoda, 1989).

The normal short-term synchronization in the patient with Huntington's chorea is entirely consistent with the results from two patients with Huntington's chorea and two clinically normal daughters of a patient studied by Dengler *et al.* (1986). These results are of considerable interest when contrasted with the effects of Parkinson's disease on synchronization, discussed above. In Huntington's chorea, the ganglion cells in the putamen and caudate nucleus are grossly reduced in number and may be absent; little or no loss of cells is seen in the globus pallidus, the final co-ordinating pathway of the basal ganglion or in the subsantia nigra (Dunlap, 1927). In Parkinson's disease, however, there is a marked depigmentation and cell degeneration, particularly in the pars compacta of the substantia nigra and also in the locus coeruleus (Oppenheimer, 1976). Accompanying this is a depletion of dopamine and a reduction in the synthesis and binding of sites for γ-aminobutyric acid (GABA) in the substantia nigra (Hornykiewicz, 1982). Taken altogether the results suggest that relatively specific lesions of the basal ganglia in terms of site and perhaps neurotransmitter are responsible for the production of widely varying motor deficits and accompanying synchronization of motor unit firing observed in the present study and that of Dengler *et al.* (1986).

In conclusion, this study had provied evidence for specific central nervous pathways involved in the generation of short-term synchronization of firing seen during voluntary contractions in normal subjects. Established lesions of these pathways leads to reorganization and or changes in synchronized activity of neurones presynaptic to motoneurones and may mirror some of the developing motor deficits. The recording of synchronous EMG activity offers a new approach to studying central synaptic organization on a cellular basis in health and disease, with the advantage that no disturbance to the system is given as in stimulation studies. New signs of neurological abnormality can be expected to emerge, leading to new hypotheses for the mechanisms of motor disability and its logical treatment.

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