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MIRROR MOVEMENTS STUDIED IN A PATIENT WITH KLIPPEL–FEIL SYNDROME

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SUMMARY

1. Electromyographic (EMG) recordings have been made from upper limb muscles in a patient with well-defined congenital mirror movements occurring in association with Klippel–Feil syndrome and the results compared to those obtained in normal control subjects.

2. In the patient, liminal percutaneous electrical or magnetic brain stimulation applied over either hemisphere elicited bilateral and symmetrical short-latency muscle responses in relaxed intrinsic hand muscles. In the normal subjects unilateral brain stimulation only elicited contralateral muscle responses.

3. F response and H reflex studies for the patient's ulnar-supplied intrinsic hand muscles were normal. No crossed responses were recorded in the homologous muscles of the contralateral hand.

4. Scalp-recorded somatosensory-evoked responses following ulnar or median nerve stimulation were of normal latency and distribution in the patient.

5. In the patient, cross-correlation analysis of on-going single and multiunit needle EMGs recorded between muscles of left and right hands revealed a central peak in the cross-correlogram. No cross-correlogram peaks were found between left- and right-hand muscles in normal subjects. The magnitude and time course of the central peaks in the cross-correlograms constructed between the firing of motor units on opposite sides of the body in the patient were similar to those found in cross-correlograms constructed between the firing of motor units from muscles on the same side of the body in the patient and in normal subjects.

6. The magnitude of cross-correlogram peaks detected within a muscle and those detected between left and right homologous muscles showed a gradient in which the largest peaks were found in the intrinsic hand and forearm extensor muscles. The smallest peaks were observed in the forearm flexor muscles. No peaks were detected between left and right biceps brachii muscles. In intrinsic hand muscles, the size of the cross-correlogram peak detected between the EMGs of homologous muscle pairs was greater than that found for non-homologous muscle pairs.

7. Cutaneous reflex responses were recorded from first dorsal interosseous muscle following unilateral electrical stimulation of the digital nerves of the index finger. In the patient, this produced an early excitatory (E1) response on the stimulated side.

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Later excitatory (E2 and E3) responses, of approximately equal size and latency, were distributed bilaterally. In the normal subjects, reflex responses were confined to the stimulated side.

8. It is concluded that the mirror movements in this patient result from motor commands that are distributed to motoneurone pools on the left and right sides of the spinal cord via abnormally branched fast-conducting corticospinal tract fibres.

9. The finding of bilateral long-latency components of the cutaneous reflex in the patient strengthens the view that these components result from activity in a transcortical reflex pathway.

INTRODUCTION

Klippel–Feil syndrome comprises a short neck, impaired cervical mobility and a low hairline. It is characterized by variable fusion of the cervical or cervico-thoracic vertebrae. This skeletal abnormality is commonly associated with mirror movements of the hand muscles (Bauman, 1932), in which voluntary activation of a muscle or muscle group is replicated by an identical, but involuntary, movement in the homologous muscle of the opposite hand. These movements are observed predominantly in the distal musculature of the upper limb. Electromyographic (EMG) evidence for synchronous activation of homologous muscles has been found in three-quarters of Klippel–Feil patients (Baird, Robinson & Buckler, 1967). Various neurophysiological mechanisms of mirror movements have been proposed (Schott & Wyke, 1981; Forget, Boghen, Attig & Lamarre, 1986) but as yet no abnormal central motor pathway has been identified.

In this study we present evidence that the mirror movements in a 50-year-old patient with Klippel–Feil syndrome result from abnormally branched fast-conducting corticospinal tract fibres which project to motoneurone pools on both sides of the spinal cord.

In normal adult subjects, electrical stimulation of the index finger produces a triphasic reflex modulation of on-going muscle electrical activity recorded during voluntary contraction of ipsilateral forearm and hand muscles (Caccia, McComas, Upton & Blogg, 1973; Jenner & Stephens, 1982). In this study we have investigated the distribution of these different components of the cutaneomuscular reflex in different muscles on the two sides of the body in the patient with mirror movements. We present evidence consistent with the conclusion that the long-latency components of this reflex are transcortical and that this reflex activity is delivered to motoneurone pools on both sides of the spinal cord via abnormally branched corticospinal tract fibres.

Preliminary accounts of these experiments have been presented to the Physiological Society (Farmer, Ingram, Roche & Stephens, 1989; Farmer, Ingram & Stephens, 1990).

METHODS

Experiments were performed on a single 50-year-old female with Klippel–Feil syndrome who demonstrated well-defined mirror movements affecting predominately the distal musculature of

the upper limbs. The results have been compared with similar experiments in ten normal control subjects aged 21–39 years. Ethical committee approval and informed consent were obtained for all experiments.

Brain stimulation

Surface-recorded muscle responses to percutaneous electrical (Merton & Morton, 1980) and magnetic (Barker, Freeston, Jalinous, Merton & Morton, 1985) brain stimulation were obtained.

Percutaneous electrical brain stimulation. Single unilateral percutaneous electrical brain stimuli were applied to the scalp with the anode held over the left or the right cortical hand area and the cathode directed 5 cm anteriorly. Single capacitive discharges, decaying with a time constant of approximately 100 μs, were delivered using a high voltage stimulator (Digitimer D180), maximum output 750 V. Graded stimuli were applied from below threshold for evoking a muscle response to 90% maximal output of the stimulator.

Magnetic brain stimulation. Single time-varying magnetic pulses of 200 μs duration were delivered with a Novametrix 200 magnetic stimulator, via a twenty-six turn circular copper coil, mean diameter 10 cm, maximum coil output approximately 2 T, which was held tangentially to the scalp and centred over the vertex. The direction of current flow in the coil was chosen for preferential activation of the cerebral hemisphere being studied. Magnetic brain stimulation was also performed via a coil wound in a figure-of-eight. With the centre of this coil held tangentially to the scalp, focal stimulation of the hand area of the appropriate motor cortex could be achieved.

Experimental procedure. The experimental procedure for electrical and magnetic brain stimulation was the same. Surface EMGs were recorded simultaneously from left and right first dorsal interosseous muscles (1DI). Recordings were amplified and filtered (−3 dB at 10 Hz and 20 kHz) and recorded onto light-sensitive paper using a Medlec MS6 EMG machine. Subjects were first instructed to relax completely so that no background EMG activity was detected, even at high display gain (100 μV cm^{-1}), and the threshold muscle responses to brain stimulation obtained. In order to measure minimal motor latencies, stimulus strength was then increased to a maximum of 90% of the stimulator output and stimuli delivered while subjects were asked to abduct either the left or the right index finger so as to produce steady levels of background EMG.

M, F and H reflex responses

Surface EMGs were simultaneously recorded from both left and right first dorsal interosseous muscles. These bilateral recordings were made while electrical stimuli were delivered to the ulnar nerve at the wrist in order to produce clearly discernible M, F and H reflex responses in the stimulated hand.

Somatosensory-evoked responses

Simultaneous electroencephalogram (EEG) activity was recorded from the scalp over both left and right somatosensory cortices during unilateral electrical stimulation of either median or ulnar nerves at the left or the right wrist in turn. Stimulus intensity was just above the motor threshold for the hand muscles. The EEG activity from both left and right somatosensory cortices was then averaged time-locked to each electrical stimulus.

Cross-correlation analysis

Cross-correlation histograms were constructed between the firing of two single motor unit spike trains or between non-overlapping sections of multiunit data.

Motor unit recording. Monopolar concentric needle electrodes (Medlec type E/NO1, core area 0·019 mm^2) were inserted into the muscle(s) under study. The amplified EMG signal was heavily filtered (−3 dB at 2 and 16 kHz). The needle positions were adjusted so that either the activity of a single low threshold motor unit could be recorded in each channel or so that multiunit records containing on average three motor units were obtained. Recordings were stored on magnetic tape (Racal 4DS) for subsequent analysis.

Analysis. Times of occurrence of motor unit spikes were logged using a Sperry 50 microcomputer with a Cambridge Electronic Design 1401 laboratory interface (CED 1401). Cross-correlation histograms and cumulative sums were constructed using CED 1401 software. The statistical significance of any central peaks observed was confirmed using the criteria of Davey, Ellaway &

Stein (1986). The size of observed central cross-correlogram peaks was expressed as the index '*b*': the number of counts in the central peak (extras) divided by the total number of reference and response spikes used to construct the cross-correlogram (cf. Baker, Bremner, Cole & Stephens, 1988).

Experimental procedure. Pairs of motor unit spike trains were recorded within individual muscles using two needle electrodes inserted into either first dorsal interosseous (1DI), index finger extensor (F2 extensor), superficialis portion of index finger flexor (F2 flexor) or biceps brachii (biceps) muscles in the dominant arm. Motor unit spike trains were also recorded from pairs of different muscles with one electrode inserted into either 1DI, F2 extensor, F2 flexor or biceps on the right side and the other into the same muscle on the left side. In addition, in the patient, simultaneous multiunit EMGs were recorded from right and left 1DI and right and left abductor digiti minimi (ADM). Subjects were instructed to maintain a steady contraction of the single muscle under study or a steady co-contraction of both left and right homologous muscles such that a single motor unit recorded from each muscle discharged at a steady rate. In the case of multiunit recordings subjects were instructed to maintain a steady level of background EMG activity. Subjects were aided in these tasks by visual and auditory feedback of the unprocessed EMG signal.

Cutaneous reflexes

Cutaneous reflexes were recorded from 1DI.

Surface EMG recordings. Muscle electrical activity was recorded from first dorsal interosseous muscle using bipolar surface electrodes, amplified (−3 dB at 10 Hz and 20 kHz) and stored on magnetic tape (Racal 4DS) for subsequent analysis.

Electrical stimulation. Unilateral electrical stimuli were delivered at a strength of twice threshold for perception to the index finger of either the left or right hand. Stimuli were delivered at a rate of 3 s^{-1}, pulse width 100 μs, via ring electrodes (Medlec E/DS-K 53052).

Experimental procedure. Subjects were asked to maintain a steady abduction of both the left and right index fingers in order to produce background EMG activity of about 20% of the voluntary maximum. At the same time electrical stimuli were given to one index finger. The surface EMG signals from both left and right 1DI were rectified and averaged time-locked to each stimulus (SIGAV software, CED).

RESULTS

Mirror movements

In the patient, an isolated voluntary movement of either the left or right index finger resulted in the movement being faithfully but involuntarily reproduced by the same finger of the opposite hand. Mirroring of isolated finger movements could be demonstrated in all the digits of both hands. Combined movements involving some or all the fingers of one hand were also mirrored by the same movements of the same fingers of the opposite hand. Not all voluntary movements, however, were mirrored. Mirroring of both isolated movements and more complex movements was greatest when they involved the fingers but was less apparent for movements involving forearm, upper arm, shoulder and leg. There was no obvious asymmetry in the mirror movements. On no occasion was 'inappropriate' mirroring involving non-homologous muscles observed. Passive movements of upper limb muscles did not produce mirror movements. Tendon reflexes were normal. No crossed tendon reflexes were observed (for a detailed description of congenital mirror movements see Schott & Wyke, 1981).

Effects of unilateral electrical brain stimulation

In four normal subjects, unilateral percutaneous electrical brain stimulation over either cortical hand area produced clear short-latency responses in the contralateral 1DI. The thresholds for these responses in non-facilitated muscle ranged from 35 to

65% of the maximal output of the stimulator. No ipsilateral responses were seen (Fig. 1). In contrast, in the patient with Klippel–Feil syndrome and mirror movements, stimulation of the left motor cortex at threshold for evoking a muscle response (30% of maximal stimulator output) elicited responses of similar latency in

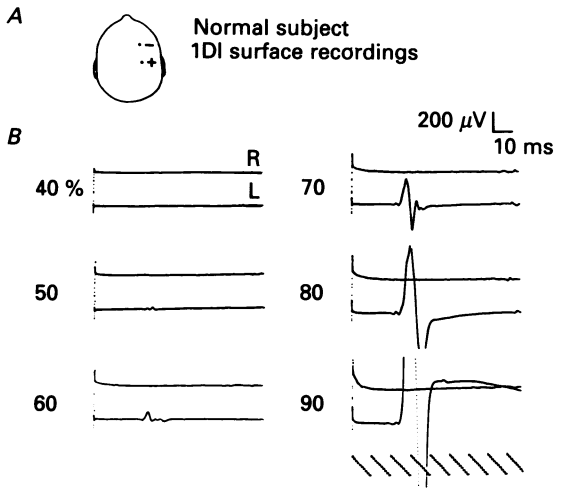

Fig. 1. *A*, stimulating arrangement for percutaneous electrical brain stimulation in both the patient and the normal subjects. The anode was situated over the hand area of the motor cortex with the cathode 5 cm anteriorly. *B*, muscle responses to transcutaneous electrical brain stimulation of the right motor cortex in a normal subject. Single sweeps of surface EMGs, triggered by the scalp stimulus, recorded simultaneously from right (upper traces) and left (lower traces) first dorsal interosseous (1DI) muscles; stimulus intensity shown as the percentage of the maximum output of the stimulator. A contralateral-evoked muscle response is observed in left first dorsal interosseous muscle only.

both left and right 1DI (Fig. 2). Increasing stimulus intensity caused bilateral increments in response amplitude and a shortening of response latency in a manner similar to that observed for the contralateral response in the normal controls. The minimal motor latencies with voluntary facilitation were 19·3 ms in the contralateral muscle and 19·8 ms in the ipsilateral muscle. Bilateral responses were also observed following unilateral electrical stimulation over the right cortex. In this case the minimal motor latencies were 19·3 ms for left 1DI and 19·7 ms for right 1DI. The mean minimal motor latency of the contralateral 1DI muscle response in normal subjects was $20{\cdot}3 \pm 2{\cdot}3$ ms (mean $\pm$ S.D.)

Effects of magnetic brain stimulation

In four normal subjects, focal magnetic stimulation only evoked muscle responses in the contralateral 1DI. In the patient with Klippel–Feil syndrome this stimulus produced responses in both left and right 1DI.

In normal subjects, the mean minimal motor latency following magnetic stimulation with the circular coil was $20{\cdot}6 \pm 1{\cdot}2$ ms for the contralateral 1DI. In the patient, the minimal motor latencies were 20·0 and 20·4 ms for right and left 1DI

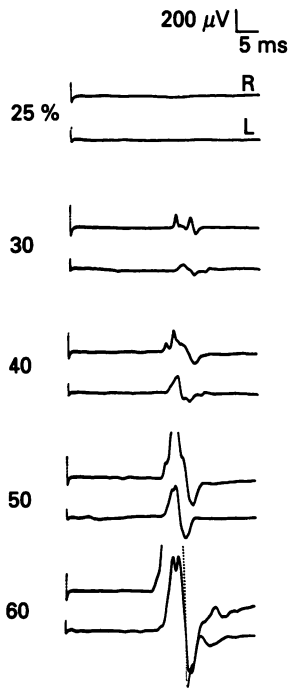

Fig. 2. Muscle responses to percutaneous electrical brain stimulation in the patient with Klippel–Feil syndrome and mirror movements. Electrical stimuli given to the scalp over the left motor cortex with the same stimulating arrangement as shown in Fig. 1*A*. Records show single sweeps of surface EMGs, triggered by the scalp stimulus, recorded simultaneously from right (upper traces) and left (lower traces) first dorsal interosseous muscles; stimulus intensity shown as the percentage of the maximum output of the stimulator. Evoked muscle responses are observed in both left and right first dorsal interossei.

following preferential activation of the left cortex; following right cortical stimulation the latencies were 20·2 ms for left 1DI and 20·4 ms for right 1DI.

M, F and H reflex responses

In the patient with Klippel–Feil syndrome, electrical stimulation of the ulnar nerve at the wrist produced large direct motor responses on the stimulated side followed by an F response. No crossed F response was recorded in the non-stimulated hand. Following stimulation of the left and right ulnar nerves the latency of the F responses recorded were in the ranges 25·8–27·4 and 25·8–28·0 ms for left and right 1DI, respectively. The H reflex was also strictly confined to the stimulated side. The latency for the H reflex detected in left 1DI following stimulation at the left wrist was 24·8 ms; stimulation at the right wrist produced an H reflex in right 1DI with a latency of 25·0 ms.

Somatosensory-evoked potential

In the normal subjects, unilateral stimulation of the median or ulnar nerve evoked a contralateral N20–P22 potential (Fig. 3*A*). On occasion, however, a small equiv-

alent potential could be identified on the ipsilateral side (see for example Fig. 3*B*). In the patient with Klippel–Feil syndrome, unilateral nerve stimulation evoked a large N20 potential on the contralateral side followed by a positivity P28 (Fig. 3*C*). On the ipsilateral side the evoked potential was small (Fig. 3*D*).

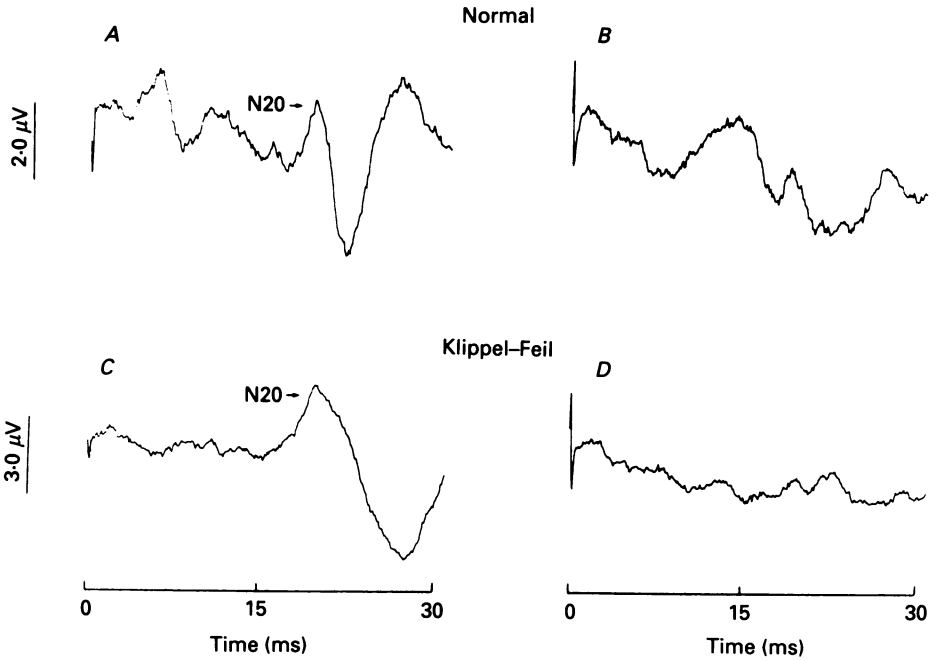

Fig. 3. *A*, contralateral somatosensory-evoked potentials recorded from the left somatosensory cortex in a normal subject following electrical stimulation of the right median nerve. *B*, averaged ipsilateral EEG recorded simultaneously from the right somatosensory cortex following the stimuli given in *A*. *C*, contralateral somatosensory-evoked potentials recorded from the left somatosensory cortex in the patient with Klippel–Feil syndrome and congenital mirror movements following electrical stimulation of the right median nerve. *D*, averaged ipsilateral EEG recorded simultaneously from the right somatosensory cortex following the stimuli given in *C*. Stimulation strength in *A*, *B*, *C* and *D* was just above motor threshold for the median nerve. *A–D*, 128 sweeps. Note in *A*, a negative peak at latency 20 ms (N20) is followed by a positive peak at 22 ms (P22). In *C*, N20 is followed by a positive peak at 28 ms (P28).

The finding of normal contralateral-evoked potentials and unenlarged ipsilateral potentials makes it unlikely that there exist in the patient bilateral projections to the cortex from the fast-conducting lemniscal afferent pathways.

Cross-correlation analysis

In all cases in four normal subjects, cross-correlation analysis of the firing of individual motor units recorded from within the same 1DI muscle revealed a peak in the cross-correlogram centred around time zero (Fig. 4*A*). The mean size (*b*) and duration of these peaks was $0{\cdot}042 \pm 0{\cdot}025$ and $13{\cdot}4 \pm 3{\cdot}5$ ms, respectively means $\pm$ S.D.; ($n = 10$ motor unit pairs). These values are similar to those reported in previous

studies for this muscle (Datta & Stephens, 1990). Cross-correlation analysis of single and multiunit activity, in which one channel (reference) contained EMGs from right 1DI and the other channel (response) contained EMGs from the left 1DI, never revealed a peak in the cross-correlogram ($n = 8$ single motor unit pairs; $n = 10$ non-overlapping sections of multiunit EMGs). This result is illustrated in Fig. 4*B* which shows, for the same subject as in Fig. 4*A*, the result of cross-correlating the firing of a motor unit in right 1DI with that of a unit in left 1DI. The peak in the cross-correlogram in Fig. 4*A* is absent in the cross-correlogram shown in Fig. 4*B*.

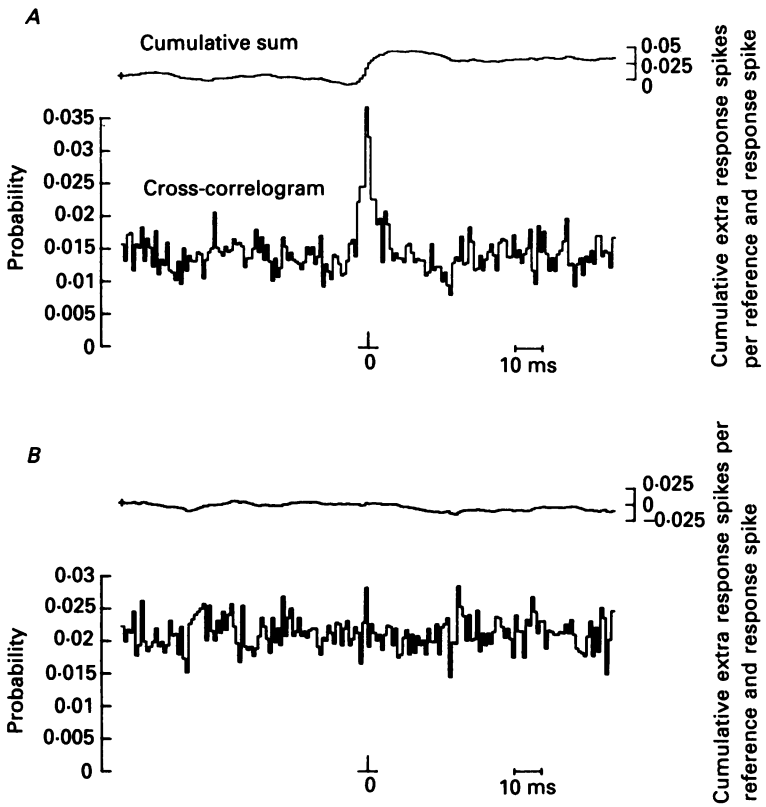

Fig. 4. *A*, cross-correlogram and cumulative sum constructed between the firing of two motor units within right 1DI, recorded during a steady voluntary contraction in a normal subject. The size (*b*) of the central cross-correlogram peak, as measured between the inflexions of the cumulative sum, was 0·051. *B*, cross-correlogram and cumulative sum constructed between the firing of a motor unit in left 1DI and one in right 1DI recorded during a steady voluntary co-contraction of both muscles. Same subject as in *A*. Number of reference spikes: 3437 in *A* and 4232 in *B*. Bin width *A* and *B*, 1 ms.

In two other normal subjects, the size and duration of the cross-correlogram peaks detected between the firing of individual motor unit pairs lying within 1DI, within F2 extensor, within F2 flexor and within biceps were compared. It can be seen from Fig. 6 (stippled bars) that the mean size (*b*) of the peak observed between the firing of motor units within these muscles diminishes when moving from 1DI to biceps. The

mean durations of the peaks were 13·2±2·1, 11·9±2·4 and 14·1±3·0 ms for 1DI, F2 extensor and F2 flexor respectively (means±S.D.).

Cross-correlation analysis between the firing of individual motor unit pairs lying within either left or right 1DI in the patient revealed a central peak in the cross-correlogram. A typical example is shown in Fig. 5*A*. The mean size (*b*) and duration of these peaks was 0·026±0·013 and 12·4±2·9 ms, respectively ($n = 5$).

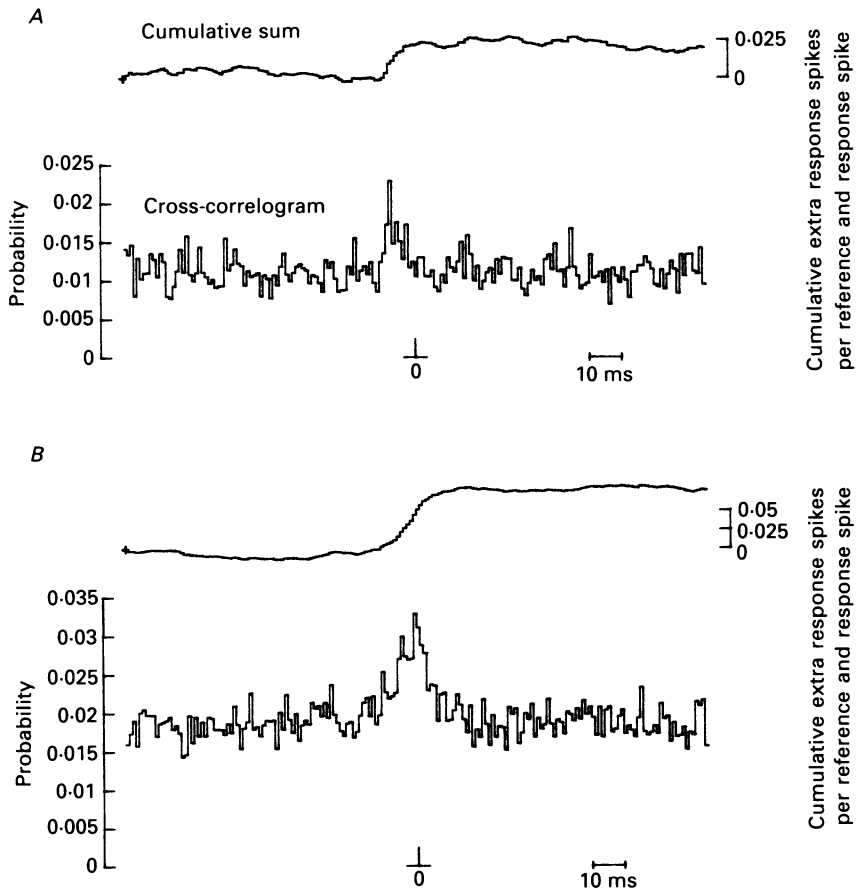

Fig. 5. *A* and *B*, cross-correlogram and cumulative sum constructed from single motor unit recordings obtained from the patient with Klippel–Feil syndrome and congenital mirror movements. *A*, motor units recorded from within left 1DI during a steady voluntary contraction. *B*, one motor unit recorded from right 1DI, the other from left 1DI during a steady voluntary co-contraction of left and right 1DI. The sizes (*b*) of the central cross-correlogram peaks in *A* and *B*, as measured between the inflexions of the cumulative sum, were 0·025 and 0·083, respectively. Number of reference spikes: 3614 in *A* and 4769 in *B*. Bin width *A* and *B*, 1 ms.

In contrast to the normal subjects, cross-correlation analysis performed between the firing of a single motor unit in the patient's right 1DI and the firing of a unit in her left 1DI revealed a peak in the cross-correlogram centred around time zero. An example is shown in Fig. 5*B*. The peaks observed in the cross-correlogram between left and right 1DI were similar in size and shape to those observed when either cross-

correlating the firing of two motor units lying within the same 1DI in normal subjects or in the patient (see Figs 4*A* and 5*A*). In the patient, a total of 10/10 left–right 1DI motor unit pairs showed a central cross-correlogram peak. Likewise 6/6 sections of non-overlapping multiunit EMGs from left and right 1DI showed a clear peak in the cross-correlogram. The mean size (*b*) of cross-correlogram peaks detected between the firing of left–right 1DI single unit pairs was $0{\cdot}036 \pm 0{\cdot}023$. The mean duration of these peaks was $19{\cdot}4 \pm 9{\cdot}7$ ms (37% of peaks in the range 4–16 ms). In the patient, the mean duration of the left–right cross-correlogram peaks was some 7 ms longer than the corresponding within-1DI peaks. This difference, however, was not statistically significant (unpaired *t* test, $P > 0{\cdot}05$; $n = 15$).

Cross-correlograms constructed between motor unit discharges recorded from within the patient's left 1DI, F2 extensor, F2 flexor and biceps were compared to those obtained when the cross-correlation was performed between discharges recorded from each of these muscles and its right-sided homologue. It can be seen in Fig. 6 that in the patient, the mean size (*b*) of the cross-correlogram peaks detected both within a muscle and between the muscle and its right-sided homologue show similar gradients, which in turn resemble the size gradient observed when the same within-muscle cross-correlations are performed in normal subjects. The mean duration of the central cross-correlogram peaks detected within left F2 extensor and within left F2 flexor were 12·2 and 11 ms, respectively. The corresponding mean peak durations detected between left and right F2 extensor and left and right F2 flexor were 16·5 and 10 ms. No central cross-correlogram peaks were detected either within left or between left and right biceps. Cross-correlation of multiunit EMGs gave qualitative support to these results: clear peaks were apparent in 6/6 multiunit records from between left and right 1DI and in 3/3 cases recorded between left and right F2 extensor; none of the cross-correlograms constructed between multiunit EMGs from left and right F2 flexor or biceps muscles showed central peaks ($n = 6$ records).

The specificity of the common synaptic inputs in the patient was investigated. Multiunit EMG recordings obtained simultaneously from right 1DI, right abductor digiti minimi (ADM), left 1DI and left ADM were subjected to cross-correlation analysis. Cross-correlograms were obtained between EMGs from the following muscle pairs: right–left 1DI, right–left ADM, right 1DI–left ADM, right ADM–left 1DI, right 1DI–ADM and left 1DI–ADM. In view of the multiunit nature of these data, the index *k* (Sears & Stagg, 1976) was chosen to express the size of the central peaks. Using this index it was found that the size of the central peak was greatest for the homologous muscle pairs right–left 1DI and right–left ADM ($k = 2{\cdot}38$ and 1·64, respectively). Cross-correlation between the non-homologous muscle pair, for example right 1DI and left ADM, revealed a peak similar in size to that observed when the cross-correlation was performed between EMGs from 1DI and ADM on the same side of the body ($k = 1{\cdot}3$ and 1·4, respectively). These results would suggest that the abnormally branched inputs access similar motoneurone pools to the non-branched inputs.

Cutaneous reflexes

Stimulation of either the left or right index finger in four normal subjects showed a clear triphasic modulation of on-going EMG activity recorded from 1DI on the

stimulated side. The configuration and latencies of these reflexes were typical of that observed in previous studies (Jenner & Stephens, 1982; Evans, Harrison & Stephens, 1989). The latency of each reflex component was measured from its point of intersection with the mean background level of EMG activity. In the normal

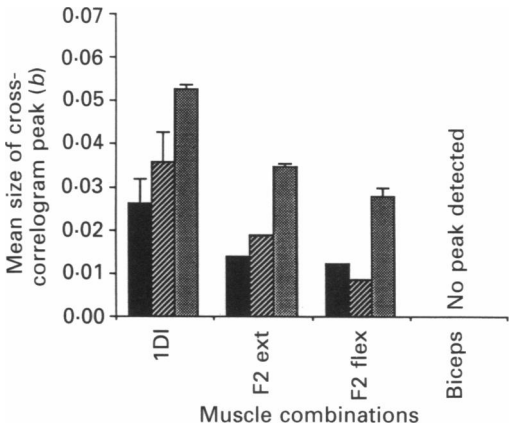

Fig. 6. Mean size (±S.E.M.) of single motor unit cross-correlogram peaks detected in different muscles in the patient with Klippel–Feil syndrome and congenital mirror movements and two normal subjects. Filled bars: mean size of central cross-correlogram peaks detected between left and right 1DI (n = 10 motor unit pairs), F2 extensor (n = 2), F2 flexor (n = 2) and biceps (n = 2) muscles in the patient. Hatched bars: mean size of central cross-correlogram peaks detected within left 1DI (n = 5), F2 extensor (n = 2), F2 flexor (n = 2) and biceps (n = 2) in the patient. Stippled bars: mean size of central cross-correlogram peaks detected within right 1DI (n = 67), F2 extensor (n = 16), F2 flexor (n = 14) and biceps (n = 5) in two normal subjects.

subjects, the mean onset latency of the early excitatory (E1) component was 32·1 ± 2·2 ms (n = 8); that of the early inhibitory (I1) component was 44·8 ± 1·6 ms (n = 8) and that of the late excitatory E2 component was 53·5 ± 1·1 ms (n = 8). One normal subject showed an excitatory E3 component, latency 80·0 ms. Simultaneous recording of on-going EMG activity from 1DI in the non-stimulated hand failed to show crossed reflex activity. A typical result for a normal subject is shown in Fig. 7*A*, and *B*.

The result of unilateral cutaneous stimulation of the right index finger in the patient with Klippel–Feil syndrome is shown in Fig. 7*C* and *D*. On the stimulated side (Fig. 7*C*) there are typical early excitatory (E1) and inhibitory (I1) components, followed by later excitatory (E2 and E3) components. The average obtained from the non-stimulated side (Fig. 7*D*) shows clear crossing of the long-latency E2 and E3 components of the reflex. There is, however, no crossing of the short-latency E1 and I1 components. A similar result was obtained when the left index finger was stimulated with crossing of the E2 and E3 components that was not accompanied by either a crossed E1 or I1 component. The magnitude of the percentage modulation of the crossed E2 response was approximately 90% of that seen on the stimulated side. The latencies of onset of the crossed and uncrossed components were similar. Cutaneous stimulation of the right index finger produced E1, I1, E2 and E3 components in right 1DI with latencies of 27, 44, 53 and 83 ms; in left 1DI the same

stimulus produced E2 and E3 components with latencies of 54 and 83 ms. Cutaneous stimulation of the left index finger produced E1, I1, E2 and E3 components in left 1DI with latencies of 32, 40, 46 and 88 ms; in right 1DI the same stimulus produced E2 and E3 components with latencies of 47 and 86 ms. The latencies of the uncrossed

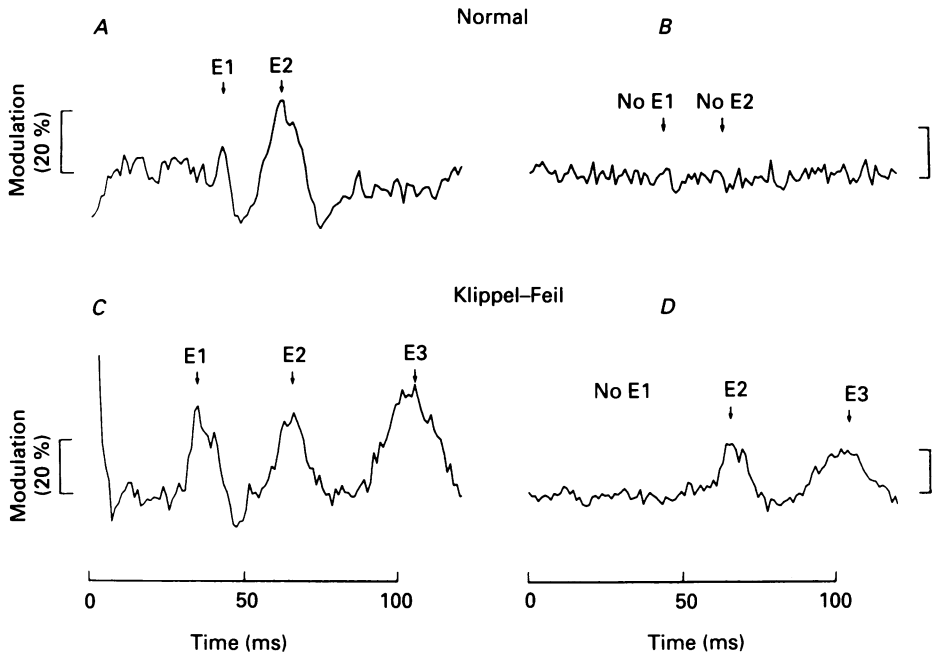

Fig. 7. *A* and *B*, averaged, rectified surface EMGs recorded from right (*A*) and left (*B*) 1DI in a normal subject. Recordings were made during steady voluntary contraction of right and left 1DI at approximately 20% of the voluntary maximum. At the same time electrical stimuli were delivered at 3 s^{-1} to the right index finger at twice threshold for perception. Simultaneous EMGs from right and left 1DI were rectified and averaged time-locked to each stimulus. The uncrossed E1 and E2 components of the cutaneous reflex are labelled. No crossed cutaneous reflex was observed in left 1DI. *C* and *D*, averaged, rectified surface EMGs recorded from right (*C*) and left (*D*) 1DI in the patient with Klippel–Feil syndrome and mirror movements during the same stimulating and recording conditions as used in *A* and *B*. The uncrossed E1, E2 and E3 cutaneous reflex components observed in right 1DI and the crossed E2 and E3 cutaneous reflex components observed in left 1DI are labelled. The calibration bars represent a 20% modulation of the pre-existing EMG level. *A* and *B*, 485 sweeps averaged; *C* and *D*, 1195 sweeps averaged.

E1 and the crossed and uncrossed E2 components were similar to both the uncrossed E1 and E2 components observed in the normal controls and to the E1 and E2 latencies previously described for index finger abduction (Evans *et al.* 1989).

DISCUSSION

Brain stimulation

The finding of bilateral short-latency muscle responses to unilateral percutaneous electrical and magnetic brain stimulation in the patient with congenital mirror

movements in association with Klippel–Feil syndrome demonstrates that there exist in this patient fast-conducting pathways from the cortex that reach homologous left- and right-hand muscles. These bilateral muscle responses displayed similar properties to the contralateral muscle responses obtained in normal subjects.

A number of possible explanations could be advanced to account for this result. First, there might exist abnormalities at the level of the lower motoneurone pool producing abnormal muscle innervation. For example, individual motoneurone axons might branch to innervate the same muscle on both sides. However, the fact that the F response is confined to the side of stimulation argues strongly against this possibility. Another alternative would be that motoneurones innervating the same muscle on the two sides are intermingled in the same motoneurone pool. These motoneurones would then be expected to share the same descending motor command therefore resulting in mirror movements and bilateral cortically evoked muscle responses. While this possibility cannot be completely excluded, the fact that the H reflex and the spinal latency cutaneous reflex both remain confined to the stimulated side makes this an unlikely explanation; it would require that the descending motor pathways projected indiscriminately within the mixed motoneurone pool, while the segmental reflex pathways would have to project specifically to only those motoneurones innervating the muscle on the stimulated side.

There might also exist abnormalities in the descending corticospinal pathway. The simplest abnormality would be that corticospinal axons branch to excite motoneurone pools innervating the same muscle on both left and right sides. The short latency of the bilateral cortically evoked muscle responses is certainly consistent with conduction in the monosynaptic corticospinal pathway which in the monkey is known to form powerful excitatory connections with hand motoneurones. Abnormal branching of these fibres would account for the observed bilateral muscle responses and, most persuasively, account for the presence of cross-correlogram peaks between motor unit activity recorded between muscles on opposite sides of the body (see below).

We should also consider the possibility of an abnormal ipsilateral corticospinal tract. In the normal subject, unilateral brain stimulation fails to produce an ipsilateral muscle response even at a high stimulation strength. This suggests that in man this pathway does not normally project to hand muscle motoneurones. This is known to be the case in the monkey where the ipsilateral corticospinal pathway has been found to project indirectly to proximal limb motoneurones rather than directly to hand motoneurones (Bernhard & Bohm, 1954; Liu & Chambers, 1964). Thus for an ipsilateral pathway to be responsible for the short-latency bilateral cortically evoked muscle responses in the patient with Klippel–Feil syndrome, it must be powerful and make abnormal direct connections with the equivalent distal muscle motoneurone pools as those innervated by the crossed pathway.

Finally we may consider the possibility that, in the patient, electrical or magnetic brain stimulation excites abnormal pathways, which in turn excite the contralateral motor cortex. Consideration of the timing of callosal transfer, however, makes this an unlikely explanation for our findings. In the monkey, the mean time taken for an electrical stimulus to the corpus callosum to evoke excitatory postsynaptic potentials in corticomotoneurones has been found to be 2·6 ms (Matsunami &

Hamada, 1984). In man, percutaneous electrical brain stimulation produces a transcallosal response beginning at a latency of between 9 and 14 ms (Asmassian & Cracco, 1987). Thus the finding in the patient that the ipsilateral muscle response following unilateral brain stimulation lagged behind the contralateral response by at most 0·5 ms indicates that transcallosal transfer was unlikely to have been the mechanism responsible for the bilateral muscle responses.

Cross-correlation analysis

A short-duration peak at time zero in the cross-correlogram constructed between the firing of two motor units can be expected to result from activity in branched-stem last-order common presynaptic input to the two motoneurones (Sears & Stagg, 1976). The time course of such short duration peaks is dependent on the time course of the underlying common postsynaptic potentials and the impulse-generating properties of motoneurones (for theoretical analysis see Kirkwood & Sears, 1978). In the patient and in the normal subjects, the time course of cross-correlogram peaks found between the firing of motor units within muscles is consistent with that predicted by Kirkwood's model on the basis of the joint arrival of unitary postsynaptic potentials from branched common-stem presynaptic fibres (for examples see Datta & Stephens, 1990). However, the duration of the cross-correlogram peaks obtained between the patient's left and right sides was on average 7·0 ms longer than that observed when motor unit activity was recorded within muscles on the same side of the body. Thus while the evidence from cortical stimulation makes it likely that the correlation between motor unit activity on the left and right sides results from activity in monosynaptic fast-conducting corticospinal pathways, before we can attribute these findings to abnormal branching of corticospinal fibres it is necessary to account for the increase in duration of some of the cross-correlogram peaks observed between the patient's left and right sides.

In principle, the increased duration of the cross-correlogram peaks observed between left and right muscles may have resulted either from temporal dispersion of presynaptic impulses (Kirkwood, Sears, Stagg & Westgaard, 1982*a*) or from the effects of presynaptic synchronization of motoneurone inputs (Kirkwood & Sears, 1978; Kirkwood, Sears, Tuck & Westgaard, 1982*b*; Smith & Fetz, 1989). Variable conduction velocities of branched presynaptic fibres, particularly with a branch site some distance rostral to the motoneurone pools, could lead to considerable temporal dispersion. Interestingly, 37% of the peaks observed between left and right were narrow (4·0–16·0 ms) and therefore had a time course that could be matched directly by the model of Kirkwood (Kirkwood & Sears, 1978). Presumably for these motoneurone pairs there was less dispersion of branched-stem conduction velocities.

An alternative to activity in branched presynaptic corticospinal axons as the cause of mirror movements in this patient, might be that there exist ipsilaterally projecting corticospinal neurones that form powerful monosynaptic connections with the equivalent motoneurone pool to that accessed by the adjacent contralaterally projecting corticospinal neurones. As discussed above, such pathways would allow both the bilateral distribution of motor commands and the detection of bilateral cortically evoked muscle responses following unilateral brain stimulation. To account for the mirror movements, the ipsilaterally and contralaterally projecting cortico-

spinal neurones would have to be active at the same time and would thus have to share some form of common input. To produce the observed peaks in the left–right cross-correlogram, the discharges from such ipsilateral and contralateral projections of the corticomotoneuronal cells would have to be strongly synchronized. In their study in the monkey, Smith & Fetz (1989) found central peaks of mean duration 21 ms in cross-correlograms constructed between the firing of pairs of corticomotoneuronal cells whose axons projected contralaterally to the same motoneurone pools. It was found that the influence of synchronization between the discharges of corticomotoneuronal cells on post-spike facilitation of EMGs and on cross-correlogram peaks detected between the firing of a corticomotoneuronal cell and a single motor unit were weak and of long duration (approximately 20 ms). By analogy we would also expect the influence of corticomotoneuronal synchronization on the cross-correlogram constructed between the firing of two motor units to be weak and of long duration. While we cannot exclude very strong and tightly time-locked corticomotoneuronal synchronization in this patient, considerations of the effects on the cross-correlograms of temporal dispersion, together with the finding of left–right cross-correlogram peaks that were narrow, with a time course consistent with the joint arrival of monosynaptic postsynaptic potentials, leads us to favour a branched corticospinal axon hypothesis for the generation of the mirror movements.

Finally, the mirror movements, the bilateral cortically evoked muscle responses and the finding of peaks in the correlograms between left and right sides may have resulted from cortical drive to an interposed population of spinal cord interneurones, whose axons project to both left and right motoneurone pools. The short latency of the bilateral muscle responses following unilateral brain stimulation and the similarity of these responses to those seen contralaterally in normal subjects makes this an unlikely possibility. In addition, as argued above, the absence of bilateral spinal-latency reflexes suggests that spinal cord circuitry *per se* is not abnormally branched in this patient.

In summary, the finding of cross-correlogram peaks between left and right muscles is evidence for the presence of abnormally branched presynaptic inputs to the corresponding motoneurone pools in the patient with mirror movements. It is likely that these branched axons are also responsible for the bilateral muscle responses to unilateral brain stimulation. The similarity of the left–right cross-correlogram peaks to those found *within* muscles in controls supports the view that in normal subjects motor unit synchronization results primarily from activity in branched axons that are of fast-conducting corticospinal origin (Datta, Farmer & Stephens, 1990).

Mirror movements

The presence of central peaks in the cross-correlogram constructed between discharges recorded from left and right hands indicates that the abnormally branched pathways are active during voluntary muscle contractions and are therefore likely to be responsible for the mirror movements. The fact that the cross-correlogram peaks were largest between left and right 1DI is consistent with the observation that the intensity of the mirror movements was greatest in the patient's distal hand muscles. Very little mirroring was observed between left and right biceps brachii; single and multiunit EMGs recorded from the two biceps muscles showed no

evidence of cross-correlated activity. Similar gradients of mean size of cross-correlogram peaks were observed for both left–right and within-muscle recordings in the patient and for within-muscle recordings in normal controls (see Fig. 6), indicating that the strength of the crossed projections is similar to that of the non-crossed projections. These observations, together with the fact that the shared input was found to be greater between homologous muscle pairs than was detected between non-homologous muscle pairs, indicates that the branched bilateral presynaptic inputs are organized in a highly similar and specific fashion. The abnormal ipsilateral branch of the corticospinal axon appears to seek out the same target motoneurone pools to those accessed by the contralateral branch. Since the two axonal branches originate from the same corticospinal neurone this circuitry would explain the observation that in this patient, it is entire motor synergies as well as individual movements that are mirrored.

In the mature central nervous system a variety of evidence suggests that the final pattern of monosynaptic projection of individual corticospinal neurones to combinations of different motoneurone pools is such as to produce a variety of muscle synergies (Fetz & Cheney, 1980, 1987; Georgopoulos, Kettner & Schwartz, 1988; Kettner, Schwartz & Georgopoulos, 1988; Lemon, 1988; Schwartz, Kettner & Georgopoulos, 1988). On this basis a particular movement is produced by a combination of activity of different corticospinal neurones each specifying an indivisible element of the movement, a different *movement* unit.

Rather as the term motor unit has been used to describe the indivisible final element of motor output for a particular muscle consisting of motoneurone and the muscle fibres it innervates, so the term movement unit describes the corticospinal motoneurone and the motoneurone pools it innervates, each motoneurone pool receiving a different strength of projection. To use Hughlings-Jackson's musical analogy, the cortex commands movements not muscles and each corticomotoneuronal cell specifies chords not notes, each note receiving a different weight. In the patient with Klippel–Feil syndrome and mirror movements an abnormality of neural development has resulted in individual corticomotoneuronal cells projecting bilaterally. The fact that whole movements such as opening and closing the hand are so accurately mirrored in this patient indicates that this bilateral branching cannot be random but must be directed to the same functionally normal pattern of motoneurone pools on the two sides. This leads us to propose that during development individual corticospinal neurones seek out a specified set of motoneurone pools. In the patient this process has been repeated bilaterally.

Cutaneous reflexes

The finding of bilateral long-latency components of the cutaneous reflex in the patient with Klippel–Feil syndrome provides further evidence that the E2 component of the cutaneous reflex results from transmission through a transcortical reflex pathway (Jenner & Stephens, 1982). The fact that cortical somatosensory-evoked potentials in this patient are normally distributed indicates that the afferent limb of this response is uncrossed. This evidence, the results of unilateral brain stimulation and cross-correlation analysis, together with the finding that the latencies of the crossed and uncrossed long-latency components were practically

identical, suggests that the long-latency E2 component is distributed bilaterally via abnormally branched fast-conducting corticospinal tract fibres. The similar appearance and latencies of the bilateral E2 components observed in the patient to those of the unilateral E2 component observed in normal subjects lends further support to the view that in normal subjects this reflex activity is also transmitted from the cortex by fast-conducting corticospinal fibres. In contrast to the neural generators of E2 and E3, the spinal neural generators of the E1 and I1 components do not appear to be abnormally branched.

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