Journal of Physiology (1992), **447**, *pp.* 755–768
With 5 *figures*
Printed in Great Britain

THE DEVELOPMENT OF CORTICO-MOTONEURONAL PROJECTIONS INVESTIGATED USING MAGNETIC BRAIN STIMULATION IN THE INFANT MACAQUE

BY D. FLAMENT, E. J. HALL AND R. N. LEMON
From the Department of Anatomy, Cambridge University, Downing Street, Cambridge CB2 3DY

(*Received 10 May 1991*)

SUMMARY

1. The effects of magnetic brain stimulation on electromyographic (EMG) activity recorded from arm and hand muscles have been investigated in five infant and six adult macaque monkeys under ketamine sedation.

2. In the adults, brief, short-latency EMG responses could be readily evoked with magnetic stimuli of 40–50% of the maximum stimulator output (1·5 T).

3. In a cross-sectional study of five infant macaques, it was difficult to evoke EMG responses in young infants (less than 5 months old). Clear short-latency reponses were first evoked in an animal 5·75 months old. This change was accompanied by an increase in the probability of occurrence of the responses.

4. In a longitudinal study of two infant monkeys over a period ranging from 2·5 to 14·5 months of age we found that clear short-latency responses were first evoked at 4 and at 5·5 months, respectively. In both animals there was a steady fall in response threshold which reached the adult range at 6·5 and 8 months, respectively. EMG responses in animals older than 8 months were indistinguishable from those in adults.

5. In the longitudinal study we also noted that the latency of EMG responses to magnetic brain stimulation declined with age. Since there were no comparable changes in the peripheral conduction time in these animals, we attribute this result to a decrease in central conduction time.

6. Parallel behavioural observations of the natural behaviour of the same animals within a colony indicated that mature precision movements of the fingers were not used until 5–6 months of age.

7. In two adult monkeys, the latency of EMG responses evoked in the extensor digitorum and first dorsal interosseous muscles by direct stimulation of the corticospinal tract, via electrodes implanted in the medullary pyramids, was found to be 0·7–1·7 ms shorter than that of responses evoked by magnetic stimuli. It is argued that at least the earliest component of these latter responses is conducted over the cortico-motoneuronal pathway.

8. The mechanisms likely to contribute to the late appearance of EMG responses to brain stimulation are discussed. One of these is probably the establishment of mature cortico-motoneuronal connections, which are not present at birth.

INTRODUCTION

The development and maturation of motor systems within the central nervous system (CNS) is a process that may not reach completion until months to years postnatally, depending on species. The age at which a given system reaches the adult level of development is linked to the phylogenetic appearance of that system (Corliss, 1976). Thus neural structures that have evolved more recently mature later than phylogenetically older structures.

In the developing motor system, this principle is illustrated by the maturation of cortico-motoneuronal (CM) connections. These connections, which provide a monosynaptic linkage between the motor cortex and spinal motoneurones, are a relatively recent feature of mammalian evolution and are well developed only amongst primates (Phillips, 1971; Heffner & Masterton, 1975). In macaque monkeys, Kuypers (1962) showed that CM projections were not present at birth and that the adult pattern of monosynaptic connections was not observed until the 6th to 8th postnatal month. Once developed, these connections provide monkeys with the capacity to perform relatively independent hand and finger movements (Lawrence & Kuypers, 1968; Kuypers, 1981). Lawrence & Hopkins (1976) found that the adult level of skill and dexterity in making relatively independent finger movements also did not appear until 6–8 months postnatally. They further showed that section of the pyramidal tract at birth prevented the maturation of such movements. These results suggest that the establishment of direct, cortico-motoneuronal connections is one of the most important factors contributing to the development of skilled hand and finger movements.

The aim of the present study was to obtain a neurophysiological measure of the functional development of the corticospinal tract and, in particular, of direct CM projections. We have employed non-invasive magnetic stimulation for this purpose. Magnetic stimulation of the monkey motor cortex has been shown to elicit short-latency EMG responses in muscles of the hand and forearm (Edgley, Eyre, Lemon & Miller, 1990) which strongly resemble those observed in man (Hess, Mills & Murray, 1986, 1987; Day, Dressler, Maertens de Noordhout, Marsden, Nakashima, Rothwell & Thompson, 1989). Edgley *et al.* (1990) have demonstrated that magnetic brain stimulation is capable of direct activation of the corticospinal tract (CST) at the level of the motor cortex in both conscious and anaesthetized macaque monkeys. Magnetic stimulation is ideally suited for the study of infant monkeys because of its non-invasive and painless nature and these factors are especially important for longitudinal studies. In the adult monkeys, we sought to establish the cortico-motoneuronal origin of the EMG responses to magnetic stimulation by comparing them to responses elicited by direct stimulation of the pyramidal tract, since this evokes CM EPSPs (cortico-motoneuronal excitatory postsynaptic potentials) in all motoneurones supplying hand and forearm muscles (Lemon, 1990).

Preliminary accounts of this study have appeared elsewhere (Flament, Hall, Lemon & Simpson, 1990*a*, *b*).

METHODS

Animal care and preparation

Experiments were carried out on five infant *Macaca mulatta* monkeys from the Rhesus colony housed in the Sub-department of Animal Behaviour, Cambridge University and on six purpose-bred adult macaques. The infants (three males: LE, HO, TH; two females: PU, JE) were aged 4·75, 5·75, 6·5, 10·25 and 12·0 months, respectively, at the time they were investigated for the cross-sectional study. Their body weights ranged from 0·85 to 3·07 kg. The adults (two male *Macaca fascicularis*: UG, MA and four females: DI, EL (*Macaca nemestrina*); KA, JO (*Macaca fascicularis*)) were between 1·5 and 10 years old and weighed 1·3–8·2 kg. We were able to follow two of the infant monkeys (LE, JE) in a longitudinal study lasting 15 months. All monkeys were sedated with ketamine (10 mg kg^{-1} I.M.) throughout the experimental procedure. Body temperature was monitored and maintained close to the normal range (37–39 °C) using a heating pad and an infra-red lamp. Experiments on the infant monkeys lasted 20–30 min. As soon as the effects of sedation had worn off, they were returned to their mothers.

Surface EMGs (electromyograms) were recorded from first dorsal interosseous (1DI), abductor pollicis brevis (AbPB), extensor digitorum communis (EDC) and deltoid (Del) muscles on the right side.

Magnetic brain stimulation

Non-invasive brain stimulation was carried out using a Novametrix 200 electromagnetic brain stimulator with a standard 9 cm mean diameter coil. Cortical stimuli delivered with this technique are painless and are not associated with adverse after-effects. Stimuli ranging from 30 to 100% of the maximum stimulator output (1·5 T) were applied in blocks of five to ten, at a rate of one shock every 2–4 s. This was repeated at each intensity in 5 or 10% increments. The coil was centred immediately above the vertex and oriented such that the current in the coil was anti-clockwise (A-side up). A comparison was made of responses elicited during periods of spontaneous, low-level muscle activity with those obtained when the muscles were relaxed (i.e. during periods of EMG silence). The latter investigation was normally done after injection of a small supplementary dose of ketamine. Data were stored on magnetic tape for later retrieval. EMG signals were full-wave rectified and then stored on a Tandon PC computer using a CED 1401 interface (SIGAVG program; CED, Science Park, Cambridge). Both single sweeps and averages were analysed, and the probability of evoking responses was calculated by determining the number of sweeps generated by a stimulus at a given strength which evoked a clear response at an appropriate latency (generally between 5 and 20 ms). The threshold for evoking these responses was defined as that which yielded clear effects in at least two of the five to ten sweeps sampled at that strength.

Ulnar nerve stimulation

To obtain a measure of peripheral conduction time we stimulated the ulnar nerve percutaneously at the elbow using a conventional electric stimulator. The latency of the responses in 1DI, together with a measurement of the distance from the medial epicondyle of the elbow to the pisiform bone at the wrist, was used to determine any significant changes in the peripheral conduction time during the period of investigation. We found no consistent differences in the conduction times measured at different ages in the two animals followed longitudinally.

Pyramidal tract electrode implantation and stimulation

Two of the adult monkeys (DI, EL) were stereotaxically implanted with pairs of fine tungsten stimulating electrodes in the medullary pyramids. Full details of this operation, which was performed under aseptic conditions and with full surgical anaesthesia, have been published previously (Lemon, Mantel & Muir, 1986). Following an initial dose of ketamine, the animals were intubated and anaesthetized with a mixture of halothane, nitrous oxide and oxygen. The electrodes were fixed in place using dental acrylic secured to the skull by stainless-steel screws. An anti-inflammatory agent (Betsolan, 0·4 mg day^{-1} I.M.) was given pre-operatively to reduce cerebral oedema. Post-operatively the animals were given a prophylactic dose of antibiotic (penicillin and streptomysin) and an analgesic (Temgesic, 0·16 mg day^{-1} I.M.) for 5 days.

Pyramidal tract stimuli, 0·2 ms in duration, were delivered singly with a repetition rate of 1·5 Hz and intensities ranging from 100 to 500 μA. These stimuli were delivered while the monkeys were sedated, and also, in separate recording sessions, during the performance of a precision grip task (Lemon *et al.* 1986). We compared the latencies of responses evoked by these stimuli with those produced by magnetic stimuli delivered during the same experimental sessions.

At the end of the experiments on these implanted monkeys, they were killed by an overdose of I.P. sodium pentobarbitone and then perfused through the heart with 0·9% saline followed by formal saline. Frozen sections of the brain stem were cut and stained. In both monkeys the tips of the electrodes were found to be positioned correctly within the pyramidal tract.

RESULTS

Responses to magnetic stimulation in adult monkeys

As shown previously (Edgley *et al.* 1990), magnetic stimulation evoked short-latency EMG responses and overt contractions from Del, EDC and 1DI in all of the adult monkeys studied. Examples of single-sweep and averaged EMG records are shown in Fig. 1*A* and *B*, respectively, from an adult (KA, approximately 10 years old).

Responses in adults were readily evoked in both relaxed and active muscles, and response thresholds were typically around 40% of the maximum stimulator output. The response latencies in different muscles are given in Table 1. Responses in intrinsic hand muscles (AbPB, 1DI) had longer latencies than those in the forearm muscle, EDC, as would be expected from the longer conduction distance. One might expect, therefore, that the most proximal muscle investigated, the deltoid, would have the shortest latency responses. However, in four of the five monkeys in which this muscle was recorded, deltoid responses had *longer* latencies than EDC (means 9·8 and 7·9 ms, respectively). The shortest latency responses in deltoid muscle were recorded in monkey DI (6·9 ms).

In two adult monkeys (DI and EL), the responses in the distal muscles to magnetic stimulation were confirmed to be cortico-motoneuronal in origin by comparing their latencies to those evoked by pyramidal tract stimulation. For EDC, 1DI and AbPB, the latency differences were small, with the magnetic responses being longer by 0·7–1·7 ms than the pyramidal responses (Table 1). This difference is comparable to the additional conduction time from motor cortex to the medullary pyramid for the fastest corticospinal axons (0·89 ms, Edgley *et al.* 1990).

Short-latency responses in deltoid to magnetic stimulation that would have been compatible with CM conduction (i.e. < 5 ms) were not observed. A small deltoid response to pyramidal shocks at 4·0 ms was observed in one monkey (DI).

Age dependence of response threshold and probability

The principal finding of the present study is that the ease with which a given muscle could be made to respond to magnetic stimulation was strongly dependent on age. In the monkeys used for the cross-sectional study, it was found that the threshold intensity for evoking an EMG response was highest in the young animals and lowest in the older and adult animals. Figure 1*C* and *D* shows examples of responses recorded from a 2·5-month-old infant (JE). These responses were obtained with 100% stimulator output, and were particularly difficult to obtain in hand muscles. Only one small response, which is the one shown in Fig. 1*C*, was observed

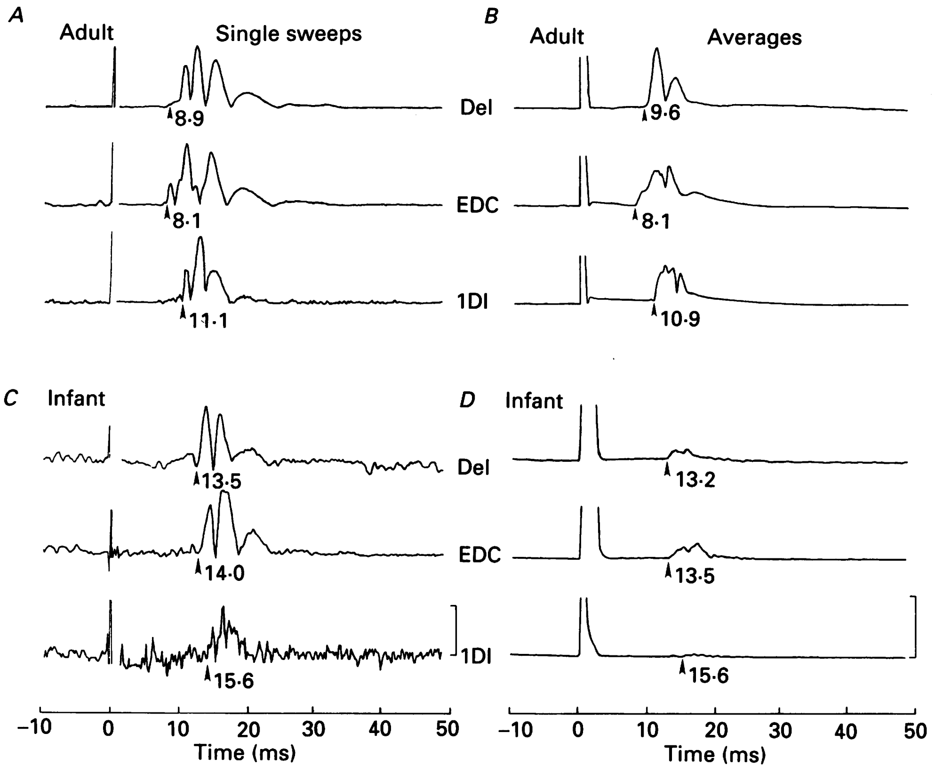


Fig. 1. EMG responses from different muscles to magnetic stimulation in adult (*A*, *B*) and infant (*C*, *D*) monkeys. Stimuli delivered during periods of spontaneous EMG activity. *A* and *C*, single-sweep responses in adult monkey KA and in the infant JE. *B* and *D*, average of ten responses in the same monkeys. Numbers at arrows are onset latencies (in ms) for responses. Del, deltoid; EDC, extensor digitorum communis; 1DI, 1st dorsal interosseous. Left vertical calibration for *A* is: Del, 1 mV; EDC, 750 μV; 1DI, 500 μV and for *C*: Del, 250 μV; EDC, 500 μV; 1DI, 30 μV. Right vertical calibration for *B* and *D*: Del, 750 μV; EDC, 750 μV and 1DI, 300 μV.

TABLE 1. Latencies (in ms) of EMG responses to magnetic and pyramidal stimuli in adult monkeys

	Magnetic stimulation			Pyramidal stimulation	
Muscle	All adults	DI	EL	DI	EL
Deltoid	9·3	6·9	—	4·0	—
EDC	7·9	7·3	7·7	6·2	6·0
AbPB	10·8	11·2	10·4	9·6	9·7
1DI	10·5	10·8	10·4	9·4	9·3

Muscles were spontaneously active during stimulation. Mean latencies for all monkeys given in far left column; $n = 5$, except for AbPB, where $n = 2$. Data from two individual adult monkeys (DI and EL) are also shown. Deltoid muscle was not investigated in monkey EL.

in 1DI of this animal. One animal (PU, 4·75 months old) showed clear responses in deltoid muscle, but none in EDC or 1DC.

Figure 2 shows plots of the changes in response threshold for 1DI as a function of age in the five infant monkeys, together with the mean adult values. Data for stimuli delivered when the muscles were relaxed and when they had some spontaneous activity are shown. Infants under 6 months of age had movement and EMG thresholds that ranged between 70 and 100% of the stimulator output and no differences were found between the relaxed or active states. Older infants and adults had thresholds as low as 35% during periods of EMG activity and even during periods of EMG silence the thresholds did not exceed 60%, with the exception of one 6-month-old infant who had a relaxed threshold of 75%. In the infants over 5 months of age, and in adult monkeys, the lowest thresholds were observed in active muscles. This point is to some extent obscured in Fig. 2 by the pooling of the adult values.

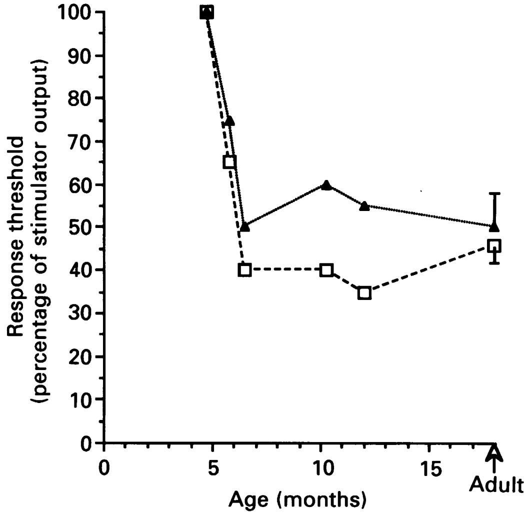


Fig. 2. Cross-sectional study: thresholds of EMG responses recorded from 1DI following magnetic brain stimuli in five infant monkeys and in five adults (DI, JO, KA, MA, UG). Responses were recorded during periods of spontaneous EMG activity (□, active) and during periods of EMG quiescence (▲, relaxed). The adult values were averaged and are displayed with standard error bars. Except in the youngest animal response thresholds tended to be 10–20% lower during periods of spontaneous activity.

Age dependence of response latency

Figure 1*B* and *D* shows that for each muscle investigated the response latencies were longer in the infant than in the adult (13·2 *vs*. 9·6 ms for Del, 13·5 *vs*. 8·1 ms for EDC, 15·6 *vs*. 10·9 ms for 1DI). In the 1DI muscle of monkeys younger than 5 months old, we rarely observed any sweeps containing responses with latencies less than 14 ms, compared to a mean value of 10·5 ms in the adults (see Table 1).

Longitudinal study

Two monkeys contributed to the longitudinal study. These animals were investigated at approximately 2 month intervals from 2·5 to 10 months of age. One monkey was examined again when it was just over 14·5 months old. The findings were similar to those reported above. Figure 3 shows the threshold data for the two monkeys. At the beginning of the study (2·5 and 3·5 months, respectively) responses were difficult to obtain, even at maximum output. Both animals then showed a decline in the threshold until 6·5 and 8 months respectively, after which no further decrease was observed; in fact, a slight increase in threshold was detected. From the earliest observations until about 5 months of age there was no difference in the response threshold for spontaneously active and relaxed muscle. Thereafter, a clear divergence appeared, with the active thresholds being consistently lower than the relaxed values, and differing by 10–20% of stimulator output.

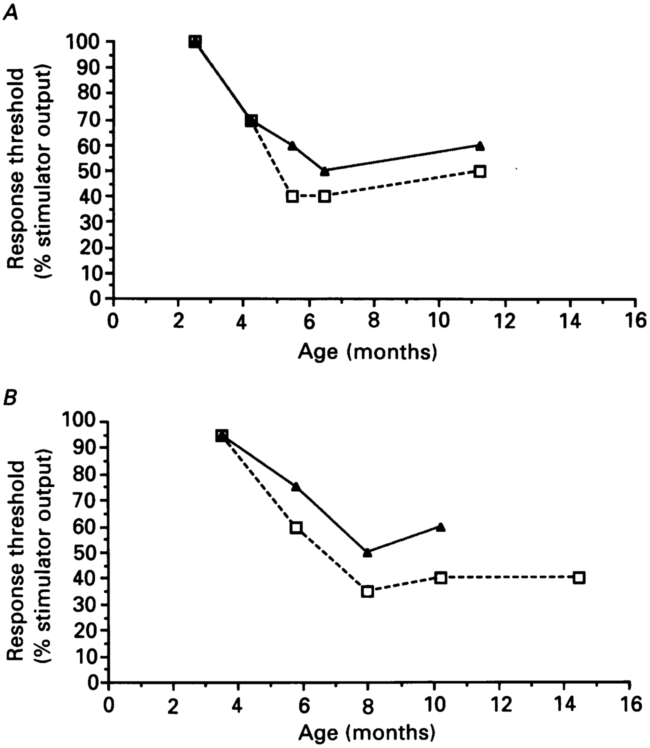
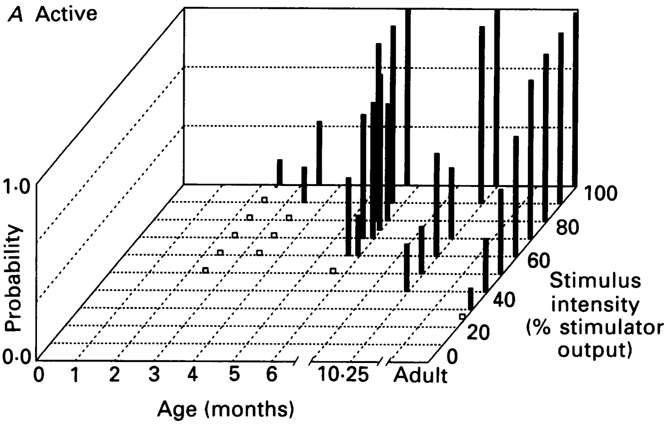


Fig. 3. Longitudinal study: thresholds of EMG responses recorded from 1DI following brain stimuli in two infant monkeys (*A*, JE; *B*, LE). Before 5 months of age the thresholds were the same for responses evoked during periods of spontaneous EMG activity (□, active) or during EMG quiescence (▲, relaxed); after this age thresholds were 10–20% lower when there was spontaneous activity. Technical problems precluded the gathering of data in the relaxed state in monkey LE at 14·5 months.

It was found that the probability of occurrence for responses to magnetic stimulation was dependent on both the age of the animal and the strength of the stimulus. The findings for 1DI from both the longitudinal and cross-sectional studies are shown in Fig. 4 and reveal that for a given suprathreshold stimulus intensity, the probability increased with increasing age and reached a maximum (i.e. 1·0) earlier (at 5·5 months) for spontaneously active muscles than for relaxed muscles (at 6 months). For an animal of a given age the probability was highest at the higher stimulus intensities and tended to plateau at intensities 20–30 % above threshold.



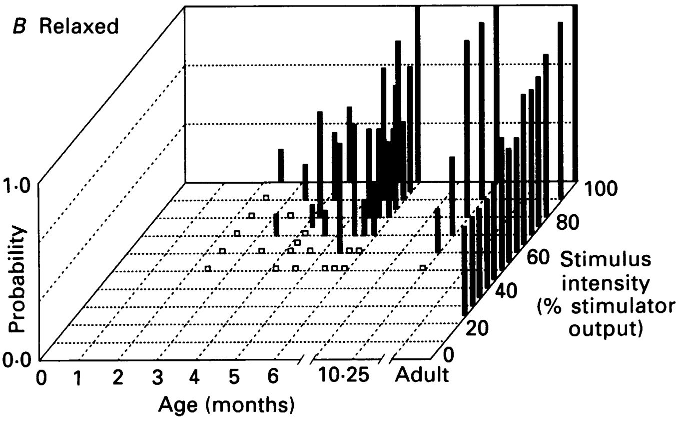


Fig. 4. Probabilities of eliciting responses in 1DI following brain stimulation. Data are taken from four infants (HO, JE, LE, PU) and include results from the longitudinal studies of JE and LE. Adult values are pooled from three monkeys over the age of 1 year (JO, LE, UG). *A*, probabilities measured when there was some spontaneous EMG activity at the time of stimulation (active) and *B*, during periods of EMG quiescence (relaxed). □, no responses observed (i.e. probability = 0). In the younger animals probabilities were low, even at high stimulus intensities. As they aged probabilities rose and responses could be elicited at lower stimulus intensities.

There was an overall decrease with age in the response latency for all muscles tested. Figure 5 illustrates this point in one of the monkeys (JE) that was followed longitudinally. At 2·5 months there was little difference in the response latency of Del, EDC and 1DI: all muscles responded at latencies between 14 and 15 ms. As the monkey matured there was a gradual decrease in the latencies of responses in these muscles, but it was particularly marked for Del and EDC. The most rapid decline in latency was at 4–6 months. In all the muscles studied we noted that, after reaching a minimum value at 6–8 months, the latencies increased slightly.

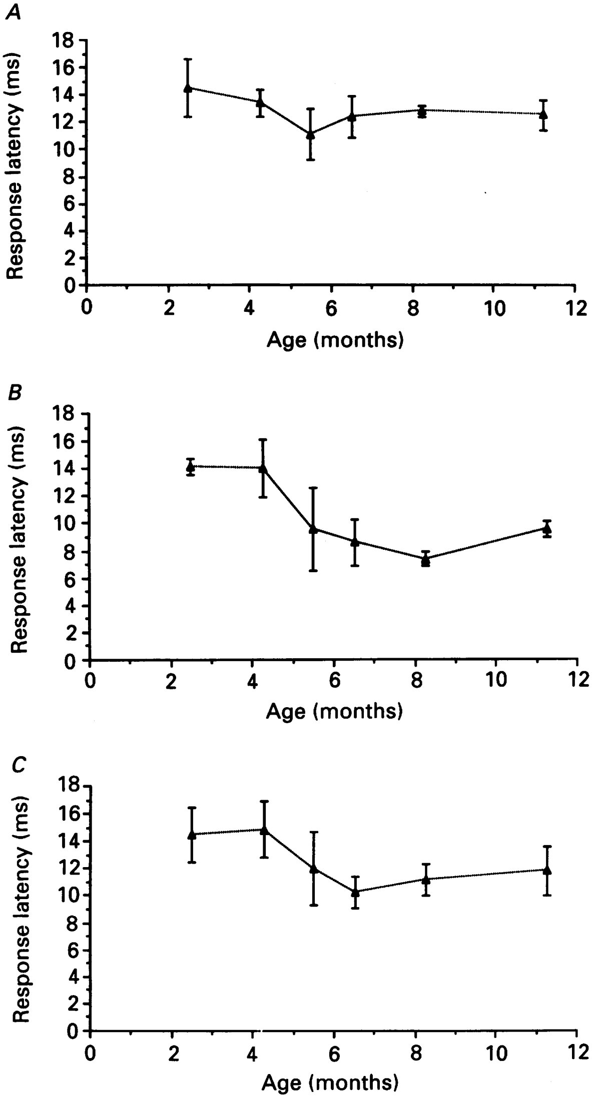


Fig. 5. Longitudinal study. Mean latency (±S.D.) of responses in 1DI (*A*), EDC (*B*) and Del (*C*) measured during periods of EMG quiescence. All data taken from monkey JE.

Behavioural observations

Four infants (aged 3–7 months) were observed while interacting freely with their mothers and in the presence of other members of their troop. Monkeys JE and LE (at 3 and 4·5 months old, respectively) spent most of their time in very close proximity to, or clinging to, their mothers. Their manual dexterity at retrieving small seeds was poor. Movements were slow and clumsy and they tended to grip between the *side* of the index finger and thumb, in contrast to adults who manipulated small seeds between the *tips* of the index and thumb. The primary, and apparently most successful, strategy for seed retrieval in these two infants was to use the tongue and lips.

Nine weeks later, JE (now 5·25 months old) had improved its performance somewhat. The adult pattern of precision grip was seen but the 'side' grip still tended to predominate. Use of the mouth for retrieving seeds was no longer evident. Monkey LE (now 6·75 months) was fully competent at making the adult precision grip between thumb and fingertip, albeit its speed of seed retrieval did not match the efficiency characteristic of adults.

Monkey PU (5·5 months old) did have the ability to make accurate precision grips of small objects. The fourth monkey, HO (7 months old) was very independent of its mother. Small seeds were gripped between the tips of the thumb and index finger. Both hands were equally skilled and used in an alternating fashion to bring food to the mouth. This rapid alternation of left and right hand was typical of the adults in the colony and was not seen in any of the younger animals.

DISCUSSION

This study demonstrates that the short-latency EMG responses evoked in a variety of arm and hand muscles by magnetic brain stimulation in adult macaques are not seen in infant monkeys. These responses are first observed in monkeys around 4 months old. The latency, threshold and probability of occurrence of these responses then undergo rapid change and become indistinguishable from those of adult macaques by around 8 months of age. These changes appear to parallel the development of relatively independent finger movements in young monkeys.

Earlier work from this laboratory has suggested that at least the earliest component of the adult EMG response to magnetic stimulation is cortico-motoneuronal in origin (Edgley *et al.* 1990). Thus, in anaesthetized macaques, magnetic stimuli elicit a large descending volley in the rapidly conducting fibres of the corticospinal tract. The amplitude of this volley indicated that with maximum output from the standard Novametrix coil (1·5 T) approximately 75% of the neurones giving rise to these fast fibres had been excited. These experiments provided strong evidence for an action of the stimuli at or very close to the cell bodies of the corticospinal neurones. In the monkey it is principally the fast fibres which give rise to the cortico-motoneuronal connections (Phillips & Porter, 1977). The present experiments confirm those of Edgley *et al.* (1990) in demonstrating that in a conscious monkey, this fast corticospinal volley elicits responses in hand and forearm muscles which have latencies very similar to those evoked by stimulation of the pyramidal tract. The small differences in latency between the two sets of responses (0·7–1·7 ms) are compatible with the extra conduction time along the corticospinal pathway from cortex to medullary pyramid. Edgley *et al.* (1990) also showed that responses evoked by magnetic stimulation had latencies comparable to those found for post-spike facilitation from identified CM cells. The existence of short-latency

EMG responses to brain stimulation can thus be taken to indicate the presence of functional cortico-motoneuronal connections.

The non-invasive method of stimulation used in this study has allowed the longitudinal development of these connections in the monkey to be followed for the first time. Some responses were present in even the youngest monkey studied (2·5 months old), but these had long latencies and low probabilities even with maximum stimulator output (Fig. 4). The two animals used showed different rates of maturation, with responses in JE (female) having a low threshold in the adult range as early as 5·5 months, while LE (male) still had relatively high thresholds at the same age, and did not show responses comparable to those in adults until 8 months. These results are in keeping with the findings of Felix & Wiesendanger (1971), who were unable to elicit short-latency responses from surface stimulation of the motor cortex in a 7-week-old monkey, although responses were obtained in a 10-month-old animal.

A number of mechanisms could explain why it is difficult to obtain short-latency responses in infant monkeys. The size difference between infant and adult brains is unlikely to be a factor, since the brain of the 2- to 3-month-old macaque is almost as large as the adult (Passingham, 1985). However, it is possible that the magnetic stimulus does not excite the motor cortex or that the corticospinal volley that is generated is not sufficiently large or synchronous to excite the spinal motoneurones. Finally, it is also possible that the slow synaptogenesis of the CM connections does not allow any short-latency excitation of forelimb muscles.

There is evidence to support the idea that some or all of these different mechanisms might be involved. It is possible that the lower responsiveness to EMS in infants is due to a lower excitability of the motor cortex. Bruce & Tatton (1980) have shown in kittens that responses in motor cortex to somatosensory input develop after motor cortex output effects can be produced by intracortical stimuli. Oka, Samejima & Yamamoto (1985) have demonstrated that immature kitten pyramidal tract neurones (PTNs) are unresponsive to thalamic inputs. These PTNs are also less able to support the generation of repetitive discharge, an important feature of the corticospinal response to non-invasive stimulation (Day, Rothwell, Thompson, Dick, Cowan, Berardelli & Marsden, 1987; Edgley *et al.* 1990). Invasive experiments will be required to determine whether magnetic stimulation does evoke descending corticospinal volleys in infant monkeys.

The myelination of the corticospinal tract is entirely postnatal. In the kitten, Oka *et al.* (1985) showed that the conduction velocity of the fastest corticospinal fibres changed dramatically in the immediate postnatal period. It is likely that the descending corticospinal volley evoked by magnetic stimulation is slower and more dispersed during the process of myelination, and that poorly myelinated fibres will tend to show a higher degree of failure at their branch points within the spinal gray (McDonald & Sears, 1970). All of these factors would interfere with the development of a short-latency, sharply rising EPSP in forelimb motoneurones in response to magnetic stimulation. Since peripheral conduction time remained approximately constant throughout the longitudinal study, it is most likely that the changes in the latency of evoked EMG responses reported here (Fig. 5) are central in origin; they may well reflect the progress of corticospinal myelination.

Kuypers's (1962) study suggested that direct, CM connections are not established until around 6–8 months of age, although he did observe some degenerating corticospinal terminals in the dorsal horn and intermediate zone of new-born macaques subjected to large lesions of the pre- and post-central gyri. We found it difficult to evoke responses in both the relaxed and active muscles of the 2- to 3-month-old monkeys, and the differences in threshold for these conditions, which are so characteristic of the adult (cf. Hess *et al.* 1987), were not observed until 4–6 months of age. This result also argues against the existence of any functional CM connections in the infant monkey, since in this case even a small descending volley could be expected to excite the target motoneurones, providing there was some background activity. Thus an alternative explanation of the latency shortening observed in this study might be a progressive change from an oligosynaptic to a monosynaptic linkage between cortex and motoneurone.

Shoulder muscles in the monkey are reported as having a small or absent CM input (Phillips & Porter, 1964; Kuypers, 1981) and in this respect it is interesting that it was relatively easy to excite the deltoid muscle in one 4·75-month-old animal, when responses in EDC and 1DI were absent. Short-latency responses, compatible with a CM input to deltoid motoneurones, were not observed in this study. For the young infant illustrated in Fig. 5, up to the age of 4 months, the mean latency of EMG responses in EDC and deltoid muscles was rather similar at around 14 ms. Although responses of both muscles subsequently became much shorter, the 1-year-old infant EDC, with the longer peripheral conduction distance, had a *shorter* latency than deltoid. This difference was also observed in the adults (Table 1). This is best explained by the late maturation of fast CM projections to EDC, which thereby overtake the oligosynaptic linkages to deltoid.

This study supports the behavioural studies of the maturation of the CM system in Rhesus monkeys (Lawrence & Kuypers, 1968; Lawrence & Hopkins, 1976). The use of relatively independent finger movements for the retrieval of food morsels does not appear until 2–3 months of age in young monkeys and fully mature movements of this type are not seen until 7–8 months of age (Lawrence & Hopkins, 1976). Grooming is another activity for which independent digit movement is essential and it is interesting that infant monkeys begin to show regular grooming behaviour at around 6 months of age (Hinde, Rowell & Spencer-Booth, 1964), i.e. at the time when the CM system appears to be approaching maturity.

This experiment was prompted by the extensive cross-sectional study of over 300 human subjects aged from 32 weeks gestation to 55 years by Eyre, Miller & Ramesh (1991), which revealed similar changes in the threshold and latency of responses to magnetic stimulation over a prolonged time course. Human infants show a rapid decrease in their central motor conduction times until around 2 years of age, which thereafter remain constant at adult values. These authors also reported a rapid decline in the threshold of EMG responses in hand and arm muscles over the same period, although thresholds continued to fall up to the age of 16 years. These results possibly reflect the protracted period of myelination of the human pyramidal tract (Yakovlev & Lecours, 1967) and the slow maturation of human hand and finger movements (Halverson, 1943). The use of magnetic brain stimulation has thus already proved to be of considerable value in exploring the neurophysiological changes underlying important behavioural developments involving the use of the hand.

This paper is dedicated to the memory of the late Professor Hans Kuypers, FRS. This work was supported by Action Research and the Medical Research Council. We gratefully acknowledge the extensive help and co-operation of Dr Michael Simpson and David Rayment of the Sub-department of Animal Behaviour, Cambridge University. We also acknowledge the collaboration of Kerry Bennett in some of these experiments. Expert technical assistance was provided by Rosalyn Cummings.

REFERENCES

BRUCE, I. C. & TATTON, W. G. (1980). Sequential output–input maturation of kitten motor cortex. *Experimental Brain Research* **39**, 411–419.

CORLISS, C. E. (1976). Elements of clinical development. In *Patten's Human Embryology*, p. 207. McGraw-Hill, New York.

DAY, B. L., DRESSLER, D., MAERTENS DE NOORDHOUT, A., MARSDEN, C. D., NAKASHIMA, K., ROTHWELL, J. C. & THOMPSON, P. D. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology* **412**, 449–473.

DAY, B. L., ROTHWELL, J. C., THOMPSON, P. D., DICK, J. P. R., COWAN, J. M. A., BERARDELLI, A. & MARSDEN, C. D. (1987). Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain* **110**, 1191–1209.

EDGLEY, S. A., EYRE, J. A., LEMON, R. N. & MILLER, S. (1990). Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *Journal of Physiology* **425**, 301–320.

EYRE, J. A., MILLER, S. & RAMESH, V. (1991). Constancy of central conduction delays during development in man: investigation of sensory and motor pathways. *Journal of Physiology* **434**, 441–452.

FELIX, D. & WIESENDANGER, M. (1971). Pyramidal and non-pyramidal motor cortical effects on distal forelimb muscles of monkeys. *Experimental Brain Research* **12**, 81–91.

FLAMENT, D., HALL, E. J., LEMON, R. N. & SIMPSON, M. (1990*a*). The development of cortically evoked muscle responses in infant macaque monkeys studied with electromagnetic brain stimulation. *Journal of Physiology* **426**, 105*P*.

FLAMENT, D., HALL, E. J., LEMON, R. N. & SIMPSON, M. (1990*b*). The development of short-latency EMG responses to electromagnetic stimulation (EMS) of the motor cortex in infant rhesus monkeys: Longitudinal and cross-sectional studies. *European Journal of Neuroscience*, suppl. 3, 65.

HALVERSON, H. M. (1943). The development of prehension in infants. In *Child Behaviour and Development*, ed. BARKER, R. G., KONNIN, J. S. & WRIGHT, H. F., pp. 49–65. McGraw-Hill, New York.

HEFFNER, R. & MASTERTON, B. (1975). Variation in the form of the pyramidal tract and its relationship to digital dexterity. *Brain, Behaviour and Evolution* **12**, 161–200.

HESS, C. W., MILLS, K. R. & MURRAY, N. M. F. (1986). Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neuroscience Letters* **71**, 235–240.

HESS, C. W., MILLS, K. R. & MURRAY, N. M. F. (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology* **388**, 397–419.

HINDE, R. A., ROWELL, T. E. & SPENCER-BOOTH, Y. (1964). Behaviour of socially living rhesus monkeys in their first six months. *Proceedings of the Zoological Society* **143**, 609–648.

KUYPERS, H. G. J. M. (1962). Corticospinal connections: postnatal development in the rhesus monkey. *Science* **138**, 678–680.

KUYPERS, H. G. J. M. (1981). Anatomy of the descending pathways. In *Handbook of Physiology*, vol. II, *The Nervous System*, ed. BROOKHART, J. M. & MOUNTCASTLE, V. B., pp. 597–666. American Physiological Society, Bethesda, MD, USA.

LAWRENCE, D. G. & HOPKINS, D. A. (1976). The development of motor control in the rhesus monkey: evidence concerning the role of corticomotoneuronal connections. *Brain* **99**, 235–254.

LAWRENCE, D. G. & KUYPERS, H. G. J. M. (1968). The functional organization of the motor system. I. The effects of bilateral pyramidal lesions. *Brain* **91**, 1–14.

LEMON, R. N. (1990). Mapping the output functions of the motor cortex. In *Signal and Sense: Local and Global Order in Perceptual Maps*, ed. EDELMAN, G., GALL, E. & COWAN, W. M., pp. 315–356. John Wiley, New York.

LEMON, R. N., MANTEL, G. W. H. & MUIR, R. B. (1986). Corticospinal facilitation of hand muscles during voluntary movement in the conscious monkey. *Journal of Physiology* **381**, 497–527.

MCDONALD, W. I. & SEARS, T. A. (1970). The effects of experimental demyelination on conduction in the central nervous system. *Brain* **93**, 583–598.

OKA, H., SAMEJIMA, A. & YAMAMOTO, T. (1985). Post-natal development of pyramidal tract neurones in kittens. *Journal of Physiology* **363**, 481–499.

PASSINGHAM, R. E. (1985). Rates of brain development in mammals including man. *Brain, Behaviour and Evolution* **26**, 167–175.

PHILLIPS, C. G. (1971). Evolution of the corticospinal tract in primates with special reference to the hand. *Proceedings of the 3rd International Congress of the Primatological Society, Zurich*, vol. 2, pp. 2–23. Karger, Basel.

PHILLIPS, C. G. & PORTER, R. (1964). The pyramidal projection to motoneurones of some muscle groups of the baboon's forelimb. In *Physiology of Spinal Cord Neurones*, ed. ECCLES, J. C. & SCHADÉ, J. P., pp. 222–242. Elsevier, Amsterdam.

PHILLIPS, C. G. & PORTER, R. (1977). *Corticospinal Neurones: Their Role in Movement.* Monograph of the Physiological Society no. 34, pp. 143–151. Academic Press, London.

YAKOVLEV, P. I. & LECOURS, A. R. (1967). Myelogenic cycles of regional maturation in the brain. In *Regional Development of the Brain in Early Life*, ed. MINKOWSKI, A., pp. 3–70. Oxford, Blackwell.