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CONSTANCY OF CENTRAL CONDUCTION DELAYS DURING DEVELOPMENT IN MAN: INVESTIGATION OF MOTOR AND SOMATOSENSORY PATHWAYS

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SUMMARY

1. A cross-sectional study has been performed on 457 normal subjects to determine changes in conduction delays with age in central and peripheral motor and somatosensory pathways to the upper limb.

2. Electromagnetic stimulation was used to investigate central and peripheral conduction in motor pathways from the cortex to biceps brachii and hypothenar muscles in 308 normal human subjects aged from 32 weeks gestation to 55 years. The responses were recorded in the surface electromyogram.

3. Somatosensory potentials evoked by electrical stimulation of the median nerve have been recorded at Erb's point and over the somatosensory cortex in 149 normal subjects aged from 34 weeks gestation to 52 years to determine central and peripheral somatosensory conduction delays.

4. The conduction delays in the central components of both motor and somatosensory pathways rapidly decrease over the first 2 years after birth and thereafter remain constant at adult values.

5. The conduction delays in the peripheral components of both motor and somatosensory pathways also decrease initially but then from the age of 5 years progressively increase in proportion to arm length.

6. The threshold stimulus intensity for evoking muscle responses following electromagnetic stimulation of the cortex is high initially and falls progressively until the age of 16 years. A linear relationship exists between the threshold intensity and height for the height range 70–180 cm.

7. The threshold stimulus intensities for exciting peripheral motor and somatosensory nerves decrease up to the age of 5 years and then reach a plateau.

8. The results support the conclusion, already reported in the literature that peripheral nerves attain maximum value for fibre diameter and conduction velocity at approximately 5 years of age.

9. In contrast, it is concluded that the maximum fibre diameters in both motor and somatosensory central pathways increase in proportion to height, leading to constant central conduction delays with growth.

INTRODUCTION

Sensorimotor integration plays an important role in the acquisition of motor skills in animals (e.g. Sakamoto, Arissian & Asanuma, 1989) and in man (e.g. Bernstein, 1967; Stelmach, 1976; Hildreth & Hollerbach, 1987; Nielson, Neilson & O'Dwyer, 1988). Such integration involves not only peripheral reflex pathways, but also occurs at many levels within the central nervous system (Lundberg, 1982; Sakamoto *et al.* 1989). The process is complex and detailed and forms the basis of internal computations within the central nervous system, as Lundberg and Oscarsson and their collaborators have demonstrated in animals (Miller & Oscarsson, 1969; Oscarsson, 1973; Lundberg, 1975, 1979 and 1982). In engineering systems, real-time controllers with feedback loops become unstable in the presence of significant transmission delays, particularly if they are variable or unpredictable (Dorf, 1986). In the light of this, one might question how stable, sensorimotor control is achieved during childhood, when stature increases by up to four times and the rate of growth varies over a twentyfold range (Figs 2*A* and 4*A*; and Tanner, Whitehouse & Takaishi, 1966). During this period of growth the nervous pathways underlying sensorimotor integration consequently undergo proportional increases in length and in their rate of change of length. To maintain stability of control during childhood, the nervous system is likely either to have constant conduction delays in these pathways or mechanisms for estimating and adjusting to changing conduction delays. The simpler solution in terms of control theory is to have brief and constant conduction delays (Dorf, 1986). To examine whether the central nervous system might make use of this solution, cross-sectional studies were undertaken on 457 subjects ranging in age from newborn babies to adults and in height from 40 to 180 cm. Measurements have been made of the central and peripheral conduction delays in motor and somatosensory systems involving the upper limb. An abstract of some of the results has been reported (Eyre, Koh, Miller, O'Sullivan & Ramesh, 1989).

METHODS

Subjects

For investigation of motor pathways, measurements were made in 308 healthy normal subjects ranging in age from 32 weeks gestation to 55 years. Somatosensory pathways were investigated in 149 healthy normal subjects ranging in age from 34 weeks gestation to 52 years. Ethical approval from Newcastle upon Tyne Joint Ethics Committee and written, informed consent from the subject or, if appropriate, the subject's parent, were obtained. Height and arm length (vertebra prominens to tip of middle finger) were measured in each subject. In a further group of seventy-seven subjects, distributed in age from 40 weeks gestation to 60 years, measurements were made of the distance from vertex (peak of skull in coronal plane vertically above the external auditory meatus) to the vertebra prominens, following the contours of the skull. In a sample of eleven adult cadavers, the length of the corticospinal pathway from the hand area of the motor cortex to the middle of the 7th cervical segment scaled as 0·75 times this distance (S. Miller, unpublished observations).

Motor pathways

Electromagnetic stimulation (MagStim 200) was used to estimate conduction delays from the motor cortex to biceps brachii and hypothenar muscles (Barker, Freeston, Jalinous & Jarrett, 1987). When the electromagnetic stimulus is applied to the brain, activity is evoked in the

corticospinal pathway (Edgley, Eyre, Lemon & Miller, 1990) which in turn activates spinal motoneurones to excite action potentials in muscle (Barker *et al.* 1987; Koh & Eyre, 1988). The electromagnetic stimulus can also be used to excite the spinal motor nerves as they emerge from the vertebral column, which enables the peripheral motor conduction delay to be measured.

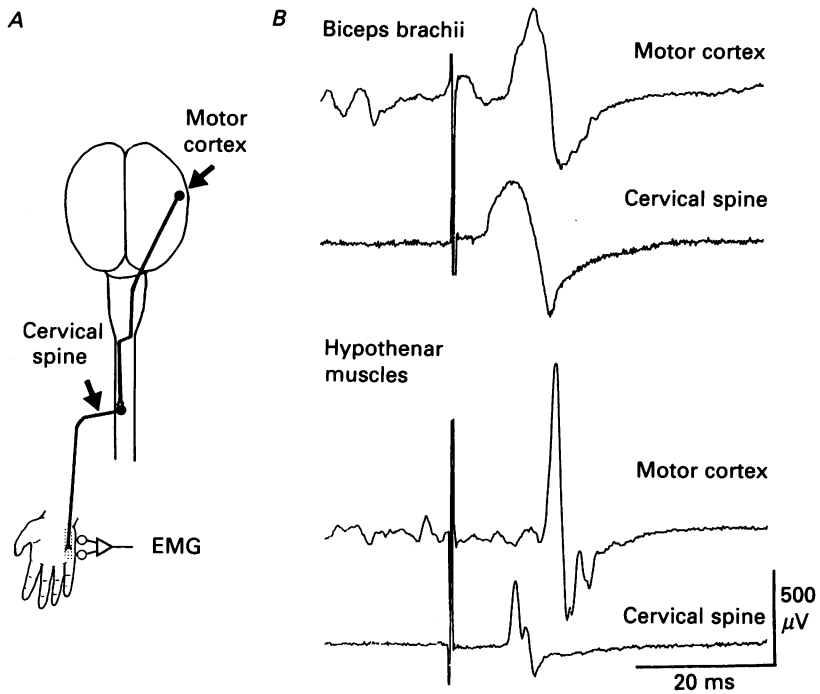

Fig. 1. Motor evoked potentials obtained in single trials from a subject aged 12 years. *A*, experimental protocol. *B*, sample records. In each pair of traces the upper record shows the response to stimulation of the motor cortex and the lower record the response to stimulation over the cervical roots.

Subtraction of the peripheral from the overall motor conduction delay thus provides an estimate of central motor conduction delay (Fig. 1; Barker *et al.* 1987; Eyre *et al.* 1989).

To stimulate the motor cortex a 9 cm circular coil was placed centrally in the tangential plane above the vertex of the head. The stimulus intensity was gradually increased until the threshold level was reached when a muscle response could be obtained in 50% of trials. The threshold level was noted and the stimulus intensity then set so that responses could be obtained in all trials. The shortest latency between cortical stimulation and the muscle response was noted.

To stimulate the cervical motor roots a 6 cm circular coil was placed in the coronal plane overlying the 5th to 8th cervical spines. As described above, the stimulus intensity was increased until the threshold level was achieved. With this stimulus intensity the coil was then moved in small steps laterally to obtain the longest latency at threshold for evoking muscle action potentials. Percutaneous electrical stimulation applied at threshold to the cervical spine has been shown to excite the motor roots close to their exit from the intervertebral foramina (Plassman & Gandevia, 1989), and it is reasonable to assume that the same applies to electromagnetic stimulation.

Electromyograms (EMGs) were recorded from left or right biceps brachii and hypothenar muscles during contraction, since Koh & Eyre (1988) have shown in children below the age of 6 years that electromagnetic stimulation of the cortex does not evoke responses in relaxed muscles. The EMG signals were recorded with skin-mounted standard Ag–AgCl EEG cup electrodes, 5 mm in diameter and with centres separated by 15 mm, amplified by a Nicolet Physiological Amplifier

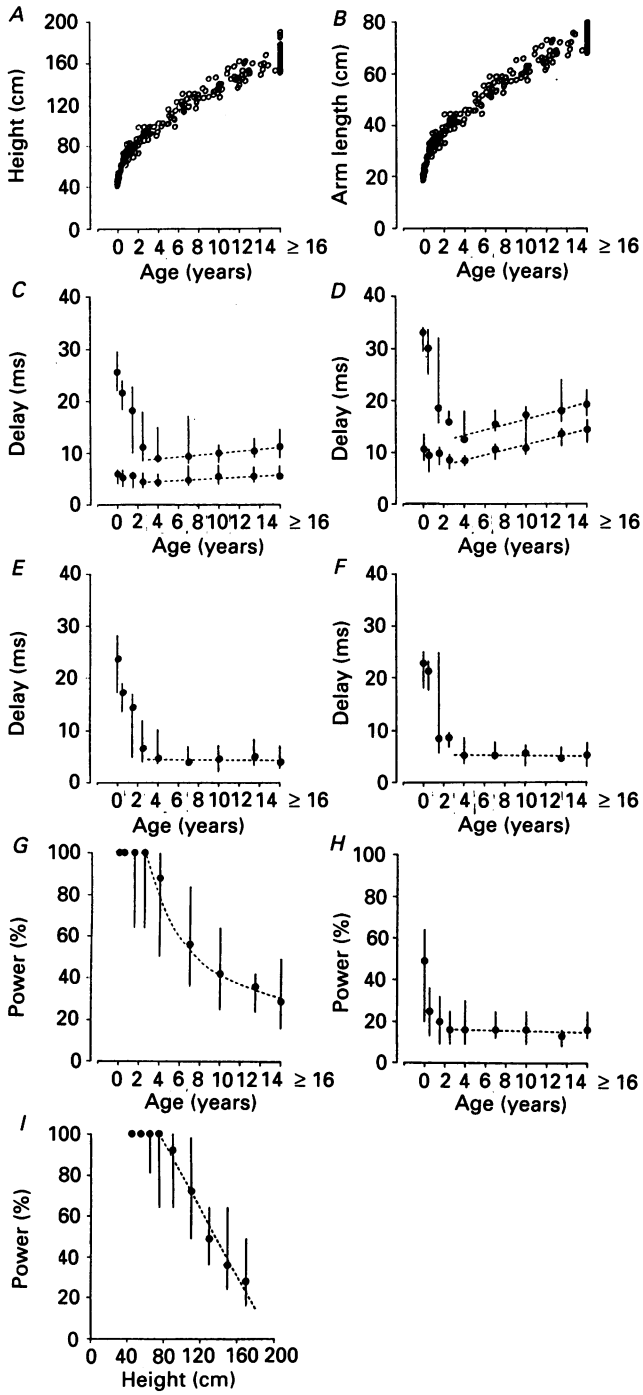

Fig. 2. Motor evoked potentials and stimulus intensity in relation to age and height in 308 subjects from birth to 55 years. *A* and *B*, height (*A*) and arm length (*B*) in relation to age. In this and all subsequent figures the $\geqslant$ 16 year point on the abscissa includes all subjects aged 16–55 years, since the values plateau at 16 years. *C* and *D*, conduction delays following stimulation of motor cortex (upper curve) and cervical spinal roots (lower curve)

(CA1000) and filtered with a −3 dB bandpass of 5–1500 Hz. The impedance of the electrodes was maintained between 1 and 5 kΩ. The signals were recorded on magnetic tape (Racal Store 4) and their latency analysed off-line by computer (Cambridge Electronic Design analysis system). The central motor conduction delay was estimated by subtracting the longest latency of onset of the muscle action potential evoked following cervical root stimulation from the shortest latency of onset of the muscle action potential evoked following cortical stimulation (Fig. 1). The stimulus intensity was expressed as the percentage of the maximum power output of the stimulator, calculated as a function of the square of the voltage fed to the coil from the stimulator output.

Somatosensory pathways

Somatosensory evoked potentials (SEPs) were evoked by electrical stimulation of the median nerve at the wrist with single pulses of 100 μs duration once per second. Using the method of Taylor & Fagan (1988) SEPs were recorded with surface electrodes overlying the brachial plexus at Erb's point, to estimate the peripheral sensory conduction delay, and on the scalp over the contralateral somatosensory cortex (C_4), to estimate the overall sensory conduction delay (Fig. 3). For both electrodes a reference of a frontal electrode, FPz, was used and all electrode impedances were maintained below 2 kΩ. Both signals were recorded simultaneously using a Nicolet Physiological Amplifier (CA1000) with a −3 dB bandpass of 5–1500 Hz and averages compiled of 256 sweeps of 50 ms duration. In each subject and for each average the stimulus intensity applied to the median nerve was increased until consistent responses were obtained at both recording sites. This level was defined as the threshold stimulus intensity and recorded in milliamperes. An estimate of the central conduction delay in somatosensory pathways was obtained by subtracting the latency of the potential at Erb's point from the latency of the first negative peak of the cortical evoked potential (Fig. 3; Hume & Cant, 1982).

RESULTS

Motor pathways

In all subjects EMG responses were obtained following both cortical and cervical stimulation (Fig. 1). During the first 2 years after birth there is a large reduction in the total and central motor conduction delay for both biceps brachii (Fig. 2*C* and *E*) and hypothenar muscles (Fig. 2*D* and *F*). From the age of 4 years a progressive increase in the total motor conduction delay occurs (Fig. 2*C* and *D*); this is attributable to the increase in peripheral motor conduction delay, which is in proportion to increasing arm length (Fig. 2*B*). In contrast, adult values for central

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to biceps brachii (*C*) and hypothenar muscles (*D*) in relation to age. In this and in subsequent graphs the filled circles indicate median values and the vertical bars the 10th to 90th centiles for age. Regression lines were calculated on raw data for each subject over the age range 4–16 years. For biceps brachii (*C*) the linear regression lines following motor cortex and cervical spine stimulation have the following values, respectively: $n = 121$, slope = 0·26 and $r = 0{\cdot}54$, and $n = 121$, slope = 0·15 and $r = 0{\cdot}40$. For hypothenar muscles (*D*) the comparable regression values are $n = 98$, slope = 0·44 and $r = 0{\cdot}64$, and $n = 98$, slope = 0·49 and $r = 0{\cdot}72$, respectively. *E* and *F*, central motor conduction delay calculated for activation of biceps brachii (*E*) and hypothenar muscles (*F*) in relation to age. Linear regression lines were calculated for the age range 3–16 years and for biceps brachii and hypothenar muscles the values are $n = 121$, slope = 0.08 and $r = 0{\cdot}10$, and $n = 98$, slope = −0·02 and $r = -0{\cdot}03$, respectively. *G* and *H*, stimulus intensity for evoking responses in biceps brachii following motor cortex (*G*) and cervical spines (*H*) stimulation in relation to age. The stimulus intensity is expressed as power and is calculated as a percentage of the maximum power output of the stimulator. The fitted curve for motor cortex stimulus intensity is $\log_{10} y = -0{\cdot}035x + 2{\cdot}04$. The linear regression of a semilog plot of stimulus intensity for cervical spine stimulation from the age of 5 years has the following values: $n = 107$, slope = −0·13 and $r = -0{\cdot}08$. *I*, stimulus intensity following motor cortex stimulation (calculated as in *G* above) in relation to height. The linear regression values are $n = 121$, slope = −0·75 and $r = -0{\cdot}78$.

motor conduction delay are achieved from the age of 2–4 years and these remain constant throughout childhood and adolescence despite a more than twofold increase in stature (Fig. 2*E* and *F*).

The threshold stimulus intensity required to excite responses through the corticospinal pathway to biceps brachii is high initially and then falls exponentially

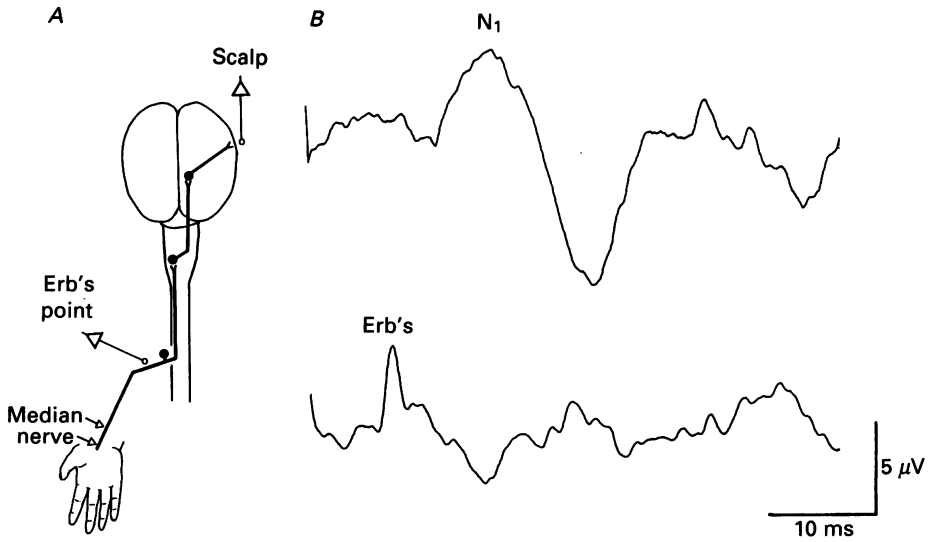

Fig. 3. Somatosensory evoked potentials were obtained in a subject aged 6 years. *A*, experimental protocol. *B*, the average of 256 responses.

with age (Fig. 2*G*); comparable results were obtained for hypothenar muscles. A linear relationship occurs between height and threshold stimulus intensity, for the height range 70–180 cm, corresponding to an age range of 2 years to adulthood (Fig. 2*I*). For excitation of cervical motor roots the threshold stimulus intensity falls rapidly over the first 2 years and then adopts adult values (Fig. 2*H*).

Somatosensory pathways

Figure 3 shows an example of SEPs recorded at Erb's point and over the somatosensory cortex in a subject of 6 years. The pattern of change of somatosensory delays with age is similar to that obtained for motor pathways. There is a large reduction in the overall somatosensory conduction delay from birth to 2 years (Fig. 4*C*). From the age of 4 years a progressive increase in the overall delay occurs; this is again attributable to the increase in peripheral conduction delay, which is also proportional to increasing arm length (Fig. 4*B*). The central somatosensory conduction delay reaches adult values at 2 years and, as with central motor conduction delay, remains constant throughout the remainder of childhood (Fig. 4*D*). The threshold stimulus intensity applied to the median nerve to evoke somatosensory potentials decreased with age to 5 years and then reached a plateau (Fig. 4*E*).

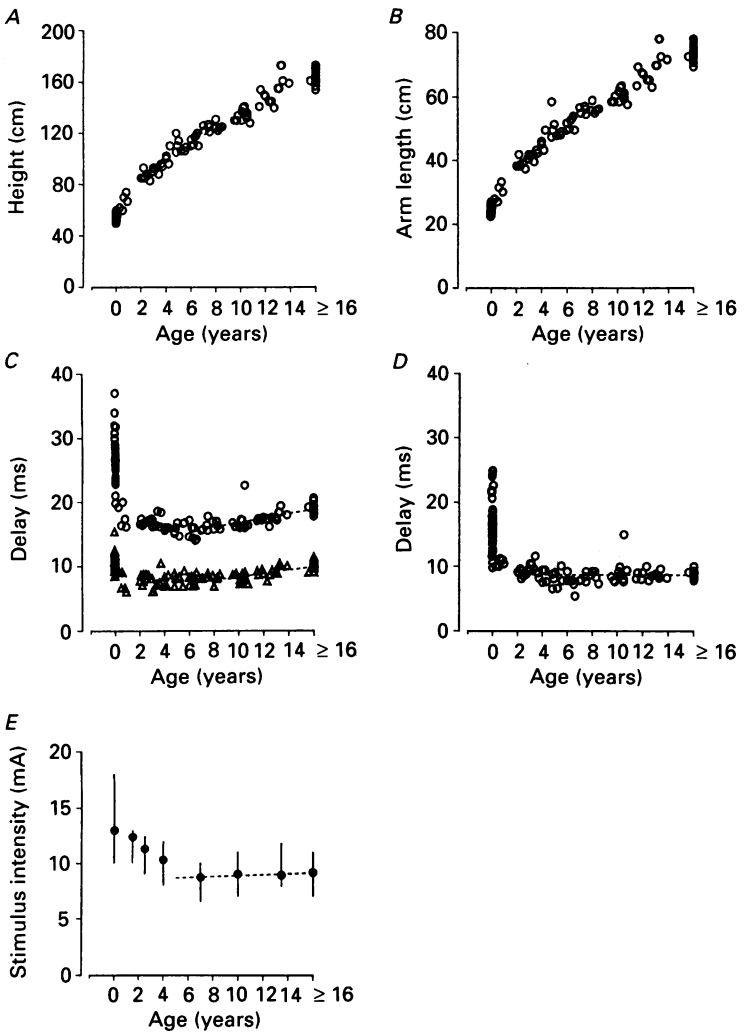

Fig. 4. Somatosensory evoked potentials in relation to age, height and stimulus intensity in 149 subjects. *A* and *B*, height (*A*) and arm length (*B*) in relation to age. *C*, somatosensory conduction delay to cortex (○) and to Erb's point (△) in relation to age. Linear regression lines were calculated over the age range 5–16 years and for cortical and Erb's responses have values, respectively, of $n = 55$, slope = 0·34 and $r = 0{\cdot}73$, and $n = 55$, slope = 0·26 and $r = 0{\cdot}79$. *D*, central somatosensory conduction delay in relation to age. Linear regression was calculated for the ages 2–16 years and has values of $n = 81$, slope = 0, $r = 0$. *E*, stimulus intensity for evoking somatosensory evoked potentials in relation to age. The filled circles indicate medians and the vertical bars the 10th to 90th centiles of the range. The linear regression line was calculated for the age range 5–16 years and has values of $n = 55$, slope = 0·04 and $r = 0{\cdot}12$.

Estimates of length of central motor and somatosensory pathways

Following the studies reported above, it was apparent that estimates of the change in length with age of central motor and somatosensory pathways were required. Measurement of the distance between vertex and vertebra prominens were therefore

made on a further group of seventy-seven healthy normal subjects from newborn to 50 years (Fig. 5). Taking the scaling factor obtained in adult cadavers (S. Miller, unpublished observations), that the measured length of the corticospinal pathway from sensorimotor cortex to C7 spinal segment is 0·75 times the distance from vertex

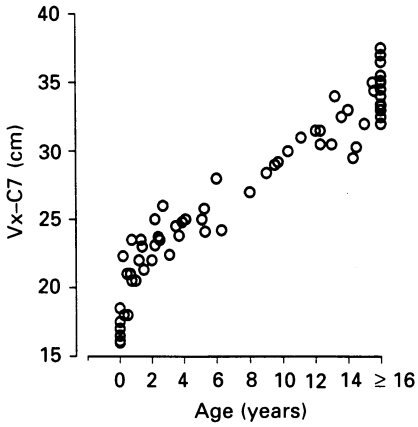

Fig. 5. Distance from vertex (Vx) to vertebra prominens (C7) in relation to age in a group of seventy-seven normal subjects.

to vertebra prominens, the central somatosensory and corticospinal pathways are likely to lengthen from approximately 17 to 27 cm over the period from 2 years to adulthood.

DISCUSSION

The present study demonstrates that the conduction delays in the central nervous components of both somatosensory and motor pathways to the upper limb fall within a narrow and consistent range from the age of approximately 2 years to adulthood despite a more than twofold increase of stature (Figs 2 and 4) and a 60% increase in pathway length (Fig. 5). In contrast, the conduction delays of the peripheral components of somatosensory and motor pathways increase gradually with age from 5 years in proportion to increasing body height and limb length (Figs 2 and 4). Different mechanisms must therefore underlie the maturation of conduction velocities during development in central and peripheral nervous pathways.

Conduction in central pathways

Central motor conduction delays have not previously been reported in children and their constancy during growth from the age of 2 years is therefore a new observation. However, there is considerable evidence from various experimental approaches that constancy of central conduction delays may be a general feature during growth and development. In a comparable study in the upper limb of somatosensory evoked potentials Taylor & Fagan (1988) obtained little change in central conduction delay (N_{12}–N_{20} peaks) from approximately 4 years to adulthood. Rowlandson & Stephens (1985) investigating the maturation of cutaneous reflexes in

the lower limb in subjects 4–16 years of age noted that the delay attributed to central reflex propagation (E_1 to E_2 peaks) remained constant. For somatosensory transmission from lumbosacral to cervical spinal levels Cracco, Cracco & Stolove (1979) reported increasing conduction velocities with age; scaling the conduction

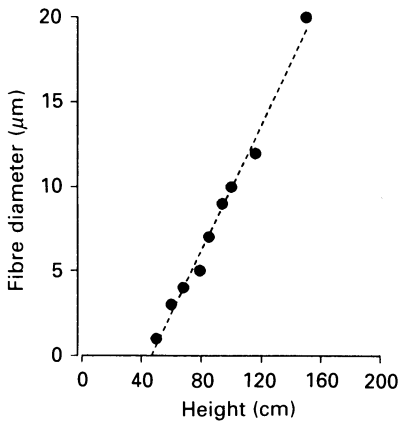

Fig. 6. Maximum fibre diameters in the corticospinal tract in relation to mean body height. The diameters of the fibres were obtained in a newborn and in subjects aged 4, 8, 18 months and 2, 3, 4 and 7 years, reported by Verhaart (1950), and in a subject aged 13 years, reported by Häggqvist (1937). The mean body height at these ages was obtained from the data of Tanner *et al.* (1966).

velocities for height reveals constant conduction delays from the age of 3 years. It should be noted that the changes with age in the length of central somatosensory and motor pathways involving the lower limb are likely to be proportionately greater than those involving the upper limb.

Constancy of central conduction delay appears not to be limited to somatosensory and motor systems. In central visual pathways the latency from stimulus to response onset in the cortex (P_1/N_1 waves) is constant during development from about 2 years (Barnet, Friedman, Weiss, Ohlrich, Shanks & Lodge, 1980; Moskowitz & Sokol, 1983). Similarly, in auditory pathways the conduction delays to brain stem (Allison, Wood & Goff, 1983) and to cortex (Barnet, Ohlich, Weiss & Shanks, 1975; Shucard, Shucard & Thomas, 1987) display adult values within the first 2 years of life.

Myelination in most fibre tracts is substantially completed in the 2–5 years after birth (Yakovlev & Lecours, 1967) and is likely to be responsible for the rapid reduction in conduction delay over this period. The constant conduction delays observed after this age would suggest, apart from possible small effects of greater synaptic efficiency, an increase in conduction velocity and therefore fibre diameter (Hursh, 1939*a*, *b*) in proportion to changing stature. The proposal that axon diameter within the central nervous system increases in proportion to height receives direct support from studies of the diameters of fibres in the human corticospinal tract in subjects varying in age from newborn babies to 13 years (Häggqvist, 1937; Verhaart, 1950; Nathan & Smith, 1955). Figure 6 shows the plot of the maximum fibre diameters reported by these authors in relation to the mean body height at the

ages of the subjects studied (Tanner *et al.* 1966) and demonstrates that the maximum fibre diameters in the corticospinal tract is linearly related to height at all ages.

In the present study the threshold for cortical activation of motor evoked potentials is related linearly to the subjects' height (Fig. 2*I*). Our studies in the monkey (Edgley *et al.* 1990) have shown that the electromagnetic stimulus directly excites corticospinal axons within the cortex. Since the threshold for exciting nerve fibres varies linearly with diameter (Kandel & Schwartz, 1985), the observed relationship of threshold for activation and height further supports the proposal that fibre diameter in the corticospinal pathway increases in proportion to body height.

Conduction in peripheral pathways

The gradual increase in conduction delays in peripheral sensory and motor nerves in proportion to limb length from the age of approximately 4 years has been documented by a variety of techniques in both sensory and motor nerves (Wagman & Lesse, 1952; Thomas & Lambert, 1960; Eisengart, 1970; Vecchierini-Blineau & Guiheneuc, 1979). Direct anatomical studies reveal that myelination in spinal roots and peripheral nerves is complete by the age of 2 years and that axon diameters attain adult values by 2–5 years after birth (Rexed, 1944; Gutrecht & Dyck, 1970). In contrast to central pathways, the fibres in peripheral nerves therefore achieve maximum conduction velocity at an early age and consequently the conduction delays in these pathways do not attain adult values until the termination of growth. The attainment of adult fibre diameters by 5 years also serves to explain in the present study the plateau at this age in the stimulus intensity required to excite the axons in the spinal motor root (Fig. 2*H*) and sensory axons in the median nerve (Fig. 4*E*).

In his theoretical paper on nerve conduction Rushton (1951) postulated that the number of nodes in a myelinated nerve fibre is the major determinant of conduction delay. Since the number of nodes in a nerve fibre remains constant during development from the onset of myelination, he proposed that conduction delays following the onset of myelination would be constant. However, his theory should apply equaly to central and peripheral myelinated nerve pathways. The findings in the present study and in other studies (Wagman & Leese, 1952; Thomas & lambert, 1960; Eisengart, 1970; Vecchierini-Blineau & Guiheneuc, 1979) of increasing peripheral conduction delays with age would be inconsistent with his proposals.

Conclusion

From the age of 2 years the fastest conducting fibres in sensory and motor central pathways operate with constant conduction delays. If this phenomenon also holds for fibres of slower conduction velocity, it may serve to provide stability of timing for such processes as internal feedback and efference copy, which have been proposed to play major roles in motor control and learning (Berstein, 1967; Stelmach, 1976; Hildreth & Hollerbach, 1987; Nielson *et al.* 1988). It is surprising that the staging of maturation is different for peripheral nerves, where early attainment of maximum fibre diameter leads to progressive changes in conduction delay with growth. Unlike central pathways, peripheral nerves are subject to uncontrolled variations of temperature and, given high Q_{10} values (*circa* 2·5, Jack, Noble & Tsien, 1983), efferent and afferent conduction delays under extreme temperature variations could be more than doubled. If precision of the timing of peripheral conduction is required

for stable sensorimotor integration and learning, some central mechanism for interactive estimation of peripheral conduction delays might be required not only during growth and development but continuously throughout life.

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