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Evidence of activity-dependent withdrawal of corticospinal projections during human development

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Article abstract—*Objective:* To characterize the development of ipsilateral corticospinal projections from birth and compare to 1) development of contralateral projections in the same subjects and 2) ipsilateral corticospinal projections in subjects with unilateral lesions of the corticospinal system acquired perinatally or in adulthood. *Methods:* Transcranial magnetic stimulation excited the motor cortex, and responses were recorded bilaterally in pectoralis major, biceps brachii, and the first dorsal interosseus muscles. Subjects studied included 9 neonates recruited at birth, studied longitudinally for 2 years; 85 healthy subjects aged from birth to adulthood; 10 subjects with hemiplegic cerebral palsy; and 8 with hemiplegia after stroke. *Results:* In neonates, ipsilateral responses had significantly shorter onsets than contralateral responses but similar thresholds and amplitudes. Thresholds within both pathways increased in the first 3 months. Differential development was present from 3 months so that by 18 months ipsilateral responses were significantly smaller and had significantly higher thresholds and longer onset latencies than contralateral responses. A similar pattern of smaller and later ipsilateral responses was observed after transcranial magnetic stimulation of the intact cortex in subjects with stroke. In contrast, subjects with hemiplegic cerebral palsy had ipsilateral responses with onsets, thresholds and amplitudes similar to those of contralateral responses. Significant branching of contralateral corticospinal axons from the intact motor cortex was excluded by cross-correlation analysis. *Conclusions:* These data, together with previously published anatomic and radiologic studies, are consistent with activity-dependent corticospinal axonal withdrawal during development and maintenance of increased corticomotoneuronal projections from the intact hemisphere after unilateral perinatal lesions.

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Corticospinal projections in several mammalian species develop transient ipsilateral projections early in development that are predominantly eliminated when maturity is reached.[1] Early unilateral lesions of the sensorimotor cortex in subprimate mammals lead to the maintenance of an increased ipsilateral corticospinal projection from the intact hemisphere. The cells of origin of these additional ipsilateral axons are distinct from and more widely distributed than the cells of origin of the crossed corticospinal projection.[1] Thus the additional ipsilateral axons do not arise solely as branches of the contralateral corticospinal axons, but arise from neurones, which project axons ipsilaterally and which would presumably withdraw these axons during normal development. The distribution of the additional ipsilateral axons within the spinal gray matter resembles that of the axons of the contralateral corticospinal projection, and synaptic contacts have been demonstrated.[2] Ipsilateral forelimb movements are observed after stimulation of the intact cortex at abnormally low current thresholds, which are abolished by medullary pyramidotomy indicating involvement of ipsilateral corticospinal axons.[3,4]

In human subjects, in which unilateral brain damage has occurred early in development, low intensity transcranial magnetic stimulation (TMS) of the intact cortex evokes large responses in ipsilateral muscles, with short onset latencies, indicating the presence of significant fast-conducting ipsilateral corticomotoneuronal projections.[5-7] These ipsilateral responses have been thought to arise from branching of the contralateral corticospinal projection from the intact hemisphere,[6] although they would also be consistent with fast conducting ipsilateral corticospinal

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projections from the intact hemisphere,[8] as has been observed in subhuman mammals.

Although the development of the contralateral corticospinal projection has been characterized in humans,[9,10] that of the ipsilateral corticospinal projection has only been studied in children aged more than 3 years.[11] It is not known, therefore, whether in humans significant ipsilateral corticospinal projections are present at birth, which are then predominantly withdrawn and which could be adaptively maintained by the intact cortex after unilateral lesions to the opposite motor cortex or its crossed corticospinal projection. The current study addresses the neurophysiologic development of the ipsilateral corticospinal tract in humans from birth in longitudinal and cross-sectional studies, providing in the same subjects comparison with the development of the contralateral corticospinal projection. The pattern of responses in ipsilateral and contralateral muscles after transcranial stimulation of the intact motor cortex in subjects with unilateral perinatal lesions (spastic hemiplegia cerebral palsy) is compared with that of subjects with hemiplegia after stroke in adulthood. Finally, cross correlation of the EMG during spontaneous co-contraction of homologous muscles was performed to consider whether ipsilateral responses arise primarily from branching of contralateral corticospinal axons from the intact hemisphere.

Methods. *Subjects.* Ethical approval was given by the Joint Ethical Committee of Newcastle upon Tyne University and the Health Authority. Informed, written consent was obtained from the subjects, and/or their parents where appropriate.

Healthy subjects. The cross-sectional study comprised 85 healthy subjects, 38 females and 47 males, aged from birth to 55 years, 18 of the subjects being neonates (8 females and 10 males). The longitudinal study comprised 9 neonates, 5 females and 4 males, first studied within 48 hours of birth and then at 3-month intervals until the age of 2 years.

Subjects with spastic hemiplegia. Subjects with spasticity were defined as those with a velocity-dependent increase in muscle tone, as part of an upper motoneurone syndrome. Subjects were chosen who had unilateral clinical signs of impaired voluntary control of both their arm and leg, with increased muscle tone, spasticity, and extensor plantar responses on the paretic side. Two subcategories were studied: those with perinatal lesions (hemiplegic cerebral palsy group) and those with lesions acquired in adulthood (stroke group).

Hemiplegic cerebral palsy group. There were 10 subjects, 7 males and 3 females, median age 11.5 years. All had the gradual postnatal development of the signs of spastic hemiplegia with no associated acute postnatal illness. One subject showed significant mirror movements (grade four severity[12]).

Stroke group. Eight adult subjects were studied, 5 men and 3 women, median age 65 years, who had had their first-ever stroke in the territory of the middle cerebral artery 6 or more months previously.

Surface electromyography. EMG of biceps brachii (biceps), clavicular fibers of pectoralis major (Pmaj), and first dorsal interosseus (FDI) were recorded bilaterally (figures 1 and 2) in healthy adults and subjects with hemiplegia. To reduce the duration of the study in babies and children responses in biceps only were studied. Bipolar Ag-AgCl skin-mounted standard EEG electrodes, 5 mm in diameter, were used with centers separated by 15 mm for babies and children up to 9 years and by 20 mm for older children and adults. The signals were fed to differential preamplifiers of 60 dB voltage gain, 100 dB common mode rejection ratio at 50 Hz, 100 MOhm input impedance, 50 Ohm output impedance, and −3dB frequency bandpass of 10 to 1000 Hz. The signals were digitized using an intelligent interface (Cambridge Electronic Design, Cambridge UK, type 1401 plus), sampled at 5 KHz and stored on a computer for subsequent analysis.

Positioning of subjects and generation of background muscle activity. Neonates and infants up to the age of 2 years were studied while lying or while sitting on their mother's knee. Older children and adults were seated on a chair. For all subjects, the head was maintained in midline position. To study corticospinal projections to biceps, responses were obtained during episodes of spontaneous bilateral contraction in subjects aged up to 6 months. Older children and adults held weights in their supinated hands with their arms flexed to about 90° at the elbow. The weights varied between 50 and 200*g*, as judged appropriate for age and stature.

To obtain bilateral contraction of Pmaj, subjects pushed their hands together with the arms flexed at 90° and medially rotated. To contract FDI the index finger and thumb were adducted against fixed resistance provided by small wooden blocks. For each muscle the EMG was also rectified and integrated (time constant 1 s) and displayed as a horizontal line on an oscilloscope. The maximum voluntary contraction (MVC) of each muscle was recorded as the greatest level of rectified, integrated EMG during bilateral contraction of homologous muscles, obtained by the subject in three attempts separated by 1minute rest intervals. During testing the subject contracted homologous muscles on opposite sides to raise the EMG displays to meet target lines set at 10% MVC.

Excitation of motor pathways. Corticospinal tracts. Transcranial magnetic stimulation (Magstim Company Ltd., Whitland, Wales), using a figure of eight coil with each circle having a diameter of 55 mm (SPC-ENG 8618, MagStim Company Ltd., Whitland, Wales), was used to excite corticospinal neurones.[13,14] The handle of the stimulating coil was placed posteriorly and parallel to the parasagittal axis.[15] To ensure accurate and reproducible coil placement a flexible, latex-coated nylon 0.5 × 0.5 cm grid was placed on the scalp and orientated according to anatomic landmarks based on the 10 to 20 international system of EEG electrode placement. For healthy subjects, the left motor cortex only was stimulated because there are no significant differences between the pattern of responses obtained in relation to the side stimulated or the handedness of subjects.[16]

The optimal sites for evoking responses in contracting contralateral and ipsilateral muscles were determined. To define the threshold for evoking responses, the intensity of TMS was increased until responses were evoked in the

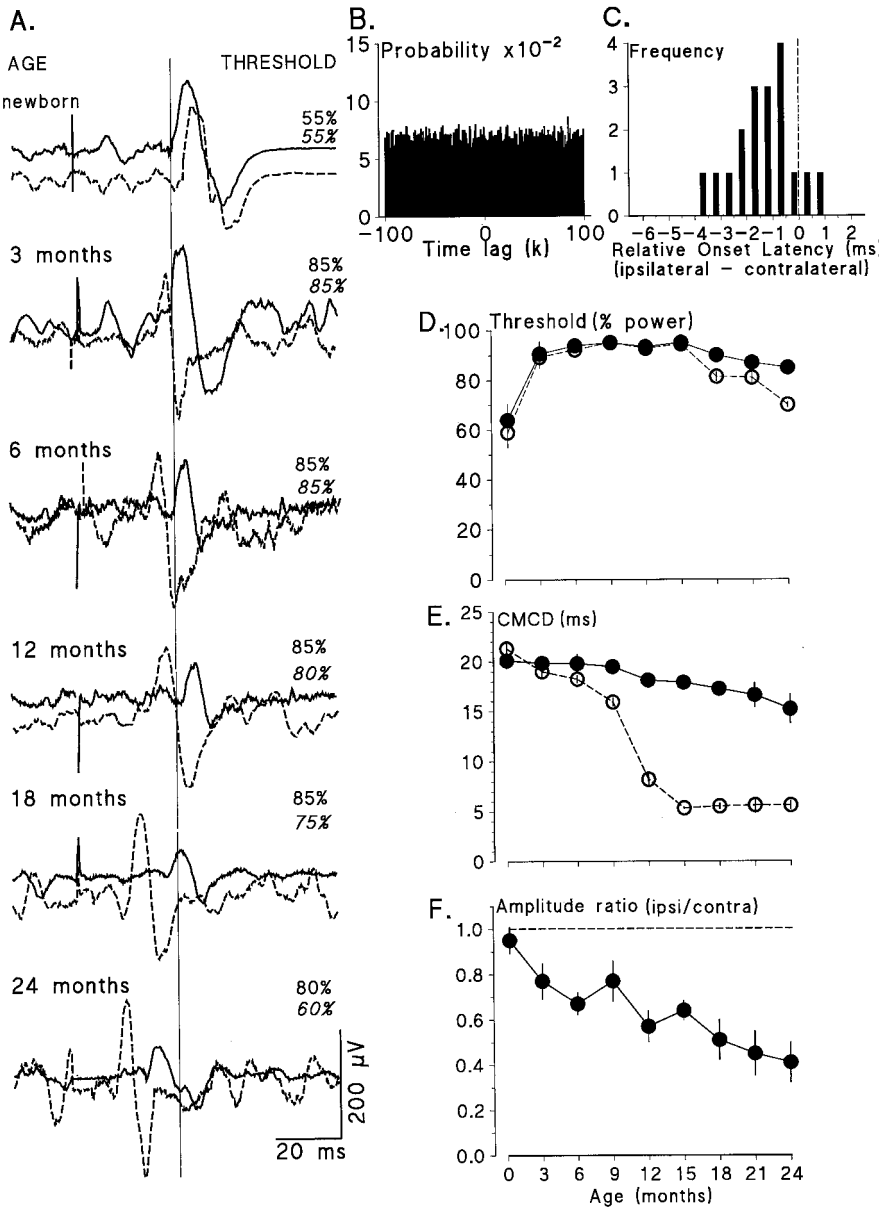

Figure 1. (A) Serial ipsilateral and contralateral responses recorded in the EMG of biceps after TMS of the left cortex in the same healthy subject at increasing ages. The continuous line traces are from ipsilateral (left) biceps and dashed line traces are from contralateral (right) biceps. The stimulus artifact marks the application of TMS. The vertical line indicates the onset of the ipsilateral response when the subject was newborn. Thresholds for the responses are recorded on the right above the traces. Those in italics are for contralateral responses. (B) Cross-correlogram of multiunit EMG from contracting right and left biceps in the same newborn subject illustrated in (A) demonstrating no evidence for common drive to the motoneuronal pools. (C) The relative onset latencies for the ipsilateral and contralateral responses in the 18 neonates studied, calculated by subtracting the onset of the ipsilateral response from that of the contralateral. (D–F) Longitudinal data from 9 subjects, including the subject illustrated in (A), studied at 3 monthly intervals. Filled symbols and continuous lines represent data from ipsilateral and open symbols and dashed lines from contralateral responses. The symbols represent the mean and the vertical lines the 95% confidence limits for mean. Threshold was measured as the percent of maximum stimulator output. The amplitude ratio was calculated by dividing the peak-to-peak amplitude of the ipsilateral responses by that of the contralateral. The horizontal dashed line in (D) indicates a ratio of one where responses are of equal size.

contracting target muscle in 50% of trials. The stimulus intensity was altered in steps of 1% except for subjects less than 2 years of age, where, to reduce the duration of each study, threshold was defined using stimulus intensity steps of 5%. At least 30 responses at 1.2 times their respective thresholds were obtained in each contralateral and ipsilateral muscle. The mean peak-to-peak amplitudes of the responses was determined and the ratio of the amplitude of the ipsilateral to the contralateral amplitudes calculated. The onset latency was defined as when the EMGclearly deviated by eye from background activity (see vertical line in figure 1A). The *shortest* onset latency was measured to estimate the total motor conduction delay (TMCD).[9]

Control for physical spread of the magnetic field to the opposite cerebral hemisphere. In all subjects, the center of the coil was placed over the left cortex, in the midline and over the right cortex at the same anterio-posterior level corresponding to the optimal site for stimulation of the left cortex. EMG was recorded in left biceps. The response frequency (the percentage of trials in which a response occurred), the onset latency of each response, and its peak-to-peak amplitude were noted for each individual in each coil position (figure 3).

Peripheral motor pathways. Magnetic stimulation using a 50 mm diameter circular coil (S/N ENG 014, MagStim Company Ltd, Whitlard, Wales) placed over the spines of C_{5-8} vertebra was used to excite spinal motor roots. The longest onset latency was determined to estimate the peripheral motor conduction delay (PMCD).[17] Subtraction of PMCD from TMCD provided an estimate of the central motor conduction delay (CMCD).

Cross-correlation analysis of the EMG of homologous muscles in the upper limb during spontaneous cocontraction. Cross-correlation analysis[6] was performed in neonates on the EMG recorded in biceps and in subjects with hemiplegic cerebral palsy on the EMG of biceps, Pmaj, and FDI. Motor unit action potentials with amplitudes exceeding the mean level of EMG by 1.96 SD were recorded as events. Cross-correlograms of 1 msec bin widths were constructed between the times of these motor unit action potentials from right and left homologous mus-

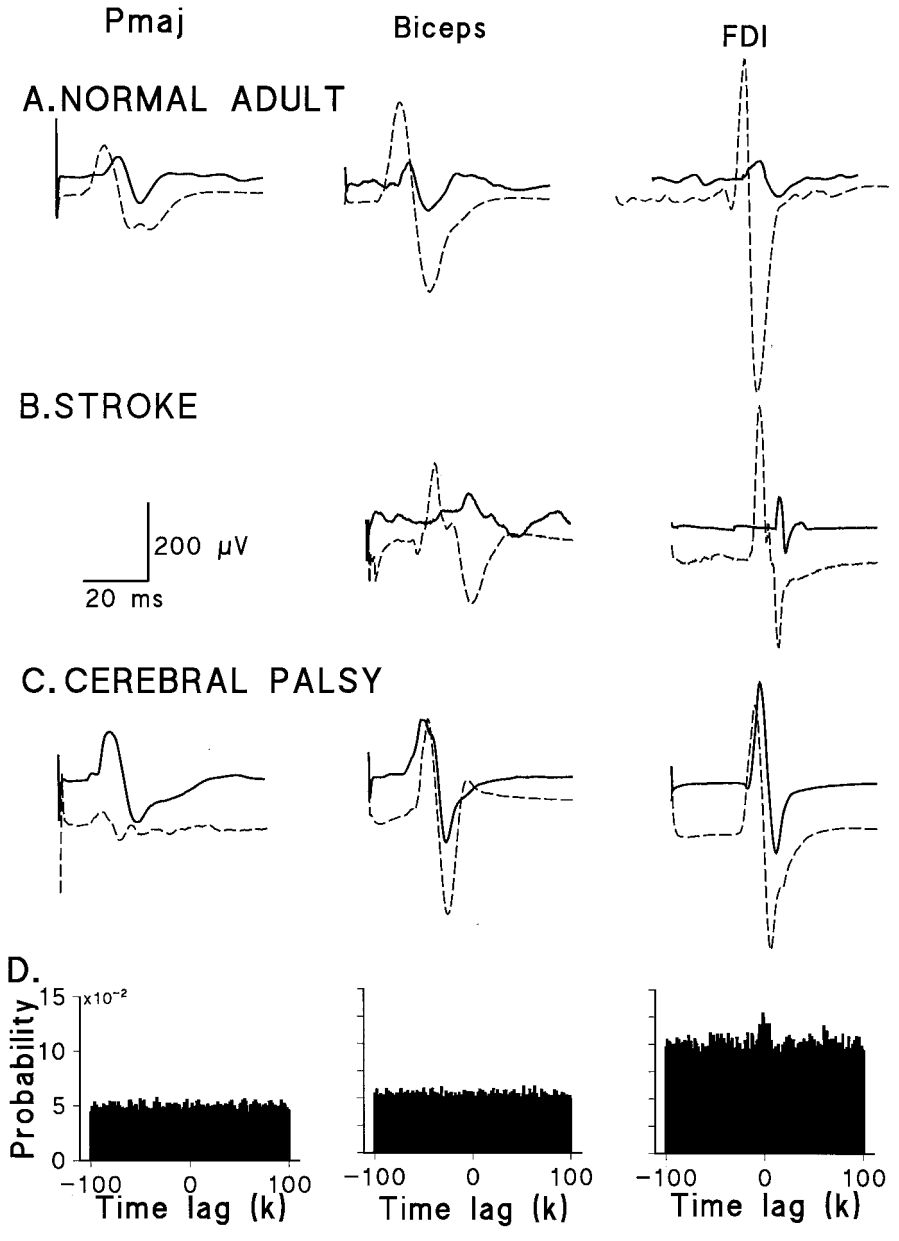

Figure 2. Ipsilateral and contralateral responses recorded in the EMG of Pmaj, Biceps, and FDI after TMS of (A) the left hemisphere in a healthy adult and the intact hemisphere in (B) a subject with stroke and (C) a subject with spastic hemiplegic cerebral palsy. The continuous traces in (A, B) and (C) are from ipsilateral muscles and dashed traces are from contralateral muscles. TMS was delivered at the onset of each trace. (D) Cross-correlograms of multiunit EMG from contracting right and left Pmaj, biceps, and FDI in the subject with spastic hemiplegic cerebral palsy and mirror movements whose responses are illustrated in (C) above. Graphs are plotted as a probability of an event from the right muscle correlating with an event in the left muscle at a time lag k.

cles (figures 1B and 2D). Continuous sequences of at least 2000 action potentials were analyzed. The size of any central peak in the cross-correlogram was determined by dividing the peak bin count by the mean bin count, to determine the synchronization index.[18] The mean bin count was calculated from the first and last 75 bins of the cross-correlogram, a region well away from any central peak.

Results. All results are expressed as means ± 95% confidence limits, and for statistical comparisons the *t*-test or contingency (χ^2) test were used.

Controls for spread of the electromagnetic stimulus to the opposite cerebral hemisphere. Midline stimulation. Five of the neonatal subjects showed responses after midline stimulation (see figure 3). The midline responses occurred with lower frequency than both ipsilateral responses after left cortex stimulation and contralateral responses after right cortex stimulation (see figure 3D; left cortex versus midline $p < 0.04$; right cortex versus midline $p < 0.01$). In addition, midline responses had smaller amplitudes (see figure 3, A through C, and 3E; left cortex versus midline $p < 0.05$; right cortex versus midline $p < 0.005$) and longer onset latencies (see figure 3, A through C, and 3F; left cortex versus midline $p < 0.005$; right cortex versus midline, $p < 0.02$). There were no significant differences in ipsilateral response rate, amplitude, and CMCD between the 5 neonates who demonstrated responses to midline stimulation and the 15 who did not (see figure 3).

Normal development of the ipsilateral responses in biceps. Ipsilateral and contralateral responses could be obtained in all subjects under the age of 12 years, whereas in adult subjects ipsilateral responses were obtained in only 7/11 (65%) of subjects.

Thresholds. The thresholds of ipsilateral and contralateral responses were not significantly different in the first 15 months after birth, although in these very young subjects the threshold was defined using the larger steps

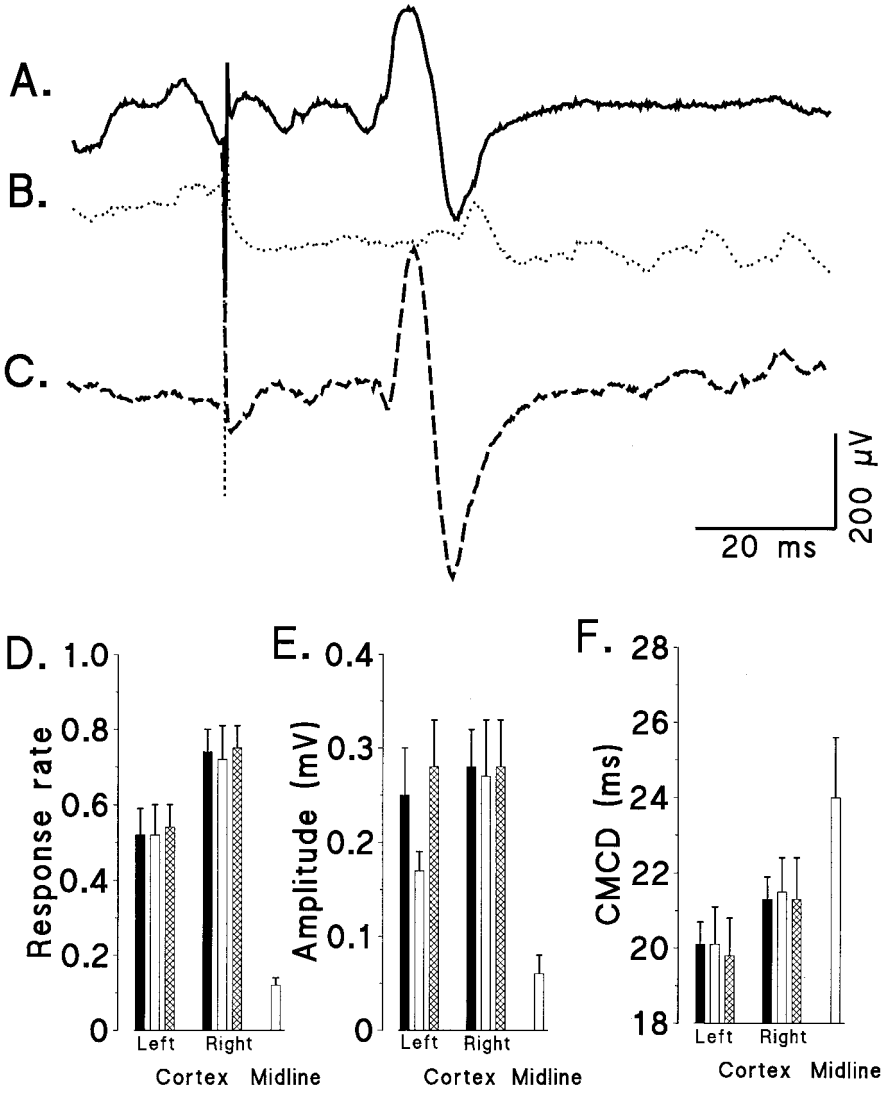

Figure 3. (A–C) Cortically evoked responses recorded from left biceps in the same neonate after TMS of (A) left (ipsilateral, continuous trace), (C) right (contralateral, dashed trace) cortex, and (B) midline (dotted trace). The stimulus artifact marks the application of TMS.(D–F) In the histograms, the solid bars represent data from all 18 neonates of the cross-sectional study, the open bars represent the data of the five babies in whom responses to midline stimulation were evoked, and the cross-hashed bars represent that of the 13 babies in whom no responses were evoked to midline stimulation. The data are expressed as means and 95% confidence limits. (D) The percentage response. (E) Amplitudes of responses. (F) Central motor conduction delay (CMCD).

of 5% stimulus output power (see figures 1, A and D, and 4J). In the first 3 postnatal months the thresholds for both ipsilateral and contralateral responses increased ($p < 0.0001$). From 12 months of age the thresholds for both responses began to decrease and continued to decrease until 16 years of age when adult values were achieved. The rate of decrease in threshold was less for ipsilateral responses, and from 15 months the ipsilateral thresholds were higher than those of contralateral responses ($p < 0.0001$).

CMCD. In neonates, the CMCD of ipsilateral responses were *shorter* than those of the contralateral (see figure 1, A through C and E, $p < 0.02$). Within individual neonates, the CMCD of ipsilateral responses occurred from 4 msec *before* to 1 msec *after* the contralateral responses (see figure 1C). CMCD decreased postnatally. The rate of decrease in CMCD was less for ipsilateral responses, which became longer than those of contralateral responses from 6 months of age (see figures 1, A and E, and 4K, $p < 0.05$).

Amplitude. There were no significant differences in the amplitudes of ipsilateral and contralateral responses in neonates (see figures 1, A and F, and 4L). Thereafter, there was a progressive reduction in the amplitude of ipsilateral compared with contralateral responses so that ipsilateral responses were smaller than contralateral responses from 3 months ($p < 0.01$). The ratio of the amplitude of ipsilateral to contralateral responses continued to decrease throughout development, until adult values were achieved at 16 years.

Ipsilateral responses in adults in proximal and distal muscles. Contralateral responses were obtained in all the adults studied in Pmaj, biceps, and FDI. The probability of obtaining ipsilateral responses decreased from proximal to distal muscles. There was no difference between the probability of obtaining a contralateral or ipsilateral response in Pmaj—11/11(100%) versus 10/11 (91%), respectively. The probability of ipsilateral responses was less than contralateral in biceps and FDI (biceps, ipsilateral 7/11 (64%) versus contralateral 11/11(100%), $\chi^2 = 4.8$, $p < 0.02$; FDI, ipsilateral 5/11 (45%) versus contralateral 11/11 (100%), $\chi^2 = 7.2$, $p < 0.01$).

Threshold. For all three muscles, the threshold for ipsilateral responses was higher than for contralateral responses (Pmaj, $p < 0.001$; biceps, $p < 0.001$; FDI, $p < 0.0001$; see figures 4A and 4J). The threshold for contralateral responses decreased along a proximal to distal gradient (Pmaj versus biceps, $p < 0.05$; Pmaj versus FDI, $p < 0.001$; biceps versus FDI, $p < 0.05$; see figure 4A). In

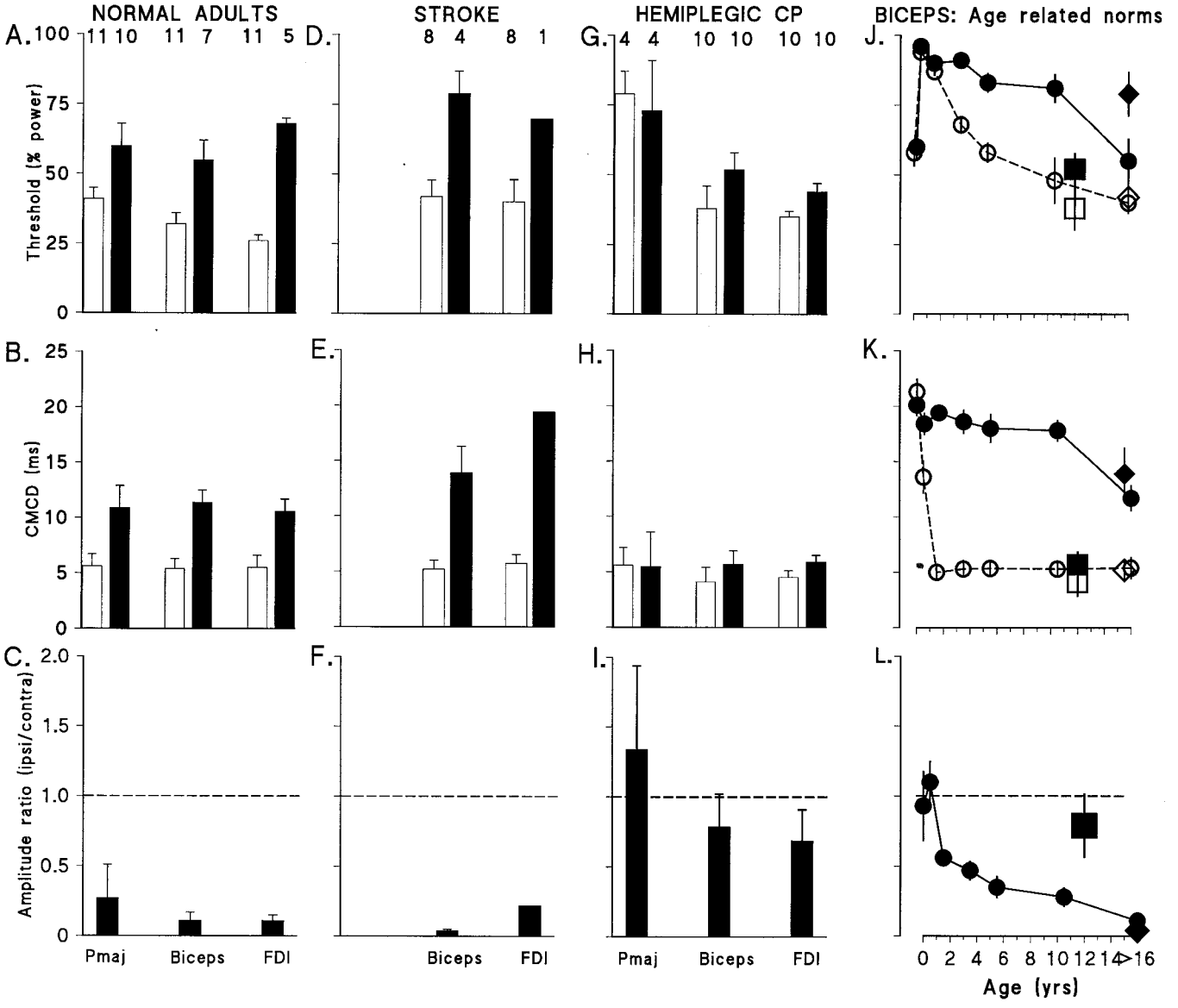

Figure 4. (A–I) Means ± 95% confidence limits for threshold (A, D, G), CMCD (B, E, H), and amplitude ratio (C, F, I) for ipsilateral responses (solid bars) and contralateral responses (open bars) evoked by TMS of the left hemisphere in healthy adults (A–C), and the intact hemisphere in subjects with hemiplegia after stroke (D–F) and those with spastic hemiplegic cerebral palsy (CP) (G–I).(J–L) Ontogeny of ipsilateral and contralateral responses in biceps muscle. Data from the cross-sectional study of 84 subjects. ● *= TMS of the left cortex in healthy subjects;* ■ *= TMS of the intact cortex in subjects with spastic hemiplegic cerebral palsy;* ♦ *= subjects with stroke. Filled symbols and continuous lines represent data from ipsilateral responses, and open symbols and dashed lines from contralateral responses. The symbols represent the mean and the vertical lines the 95% confidence limits.Threshold (A, D, G, J) was measured as the percent of maximum stimulator output. The amplitude ratio (C, F, I, L) was calculated by dividing the amplitude of the ipsilateral responses by that of the contralateral. The dashed horizontal line indicates a ratio of one where responses are of equal size.*

contrast, there was no gradient for threshold in the ipsilateral responses.

CMCD. Ipsilateral CMCD were longer than contralateral for responses evoked in all three muscles (Pmaj difference +5.6 msec, $p < 0.001$; biceps difference +7.1 msec, $p < 0.001$; FDI difference +6.6 msec, $p < 0.001$; see figures 2A and 4 B and K). For Pmaj, the difference between the onsets of ipsilateral and contralateral responses within individuals varied from −0.8 msec to +11.2 msec, for biceps from +2.0 msec to +13.2 msec, and for FDI from +2.1 msec to +8.8 msec.

Amplitude. For all three muscles, the ipsilateral responses were smaller than the contralateral responses (Pmaj, $p < 0.001$; biceps, $p < 0.001$, FDI, $p < 0.001$; see figures 2C and 4 C and L).

Ipsilateral responses in subjects with spastic hemiplegia. Responses evoked by TMS of the lesioned hemisphere. Contralateral responses could *not* be evoked in 7/10 subjects with spastic hemiplegic cerebral palsy and in 3/8 subjects with stroke. Ipsilateral responses could *not* be evoked in 9/10 of the subjects with hemiplegic cerebral palsy and in 6/8 adults with stroke. Where ipsilateral or

contralateral responses were evoked, the thresholds and CMCD were all more than three standard deviations greater than the mean value for age.

Responses evoked by TMS of the intact hemisphere. Spastic hemiplegic cerebral palsy group. Ipsilateral and contralateral responses were evoked in all subjects in the three muscles studied (see figures 2C and 4, G through I). Although the contralateral responses had thresholds and CMCD within the normal range, they were clustered below the mean value for age (see figure 4, J and K). The mean standardized deviate (or *z*-score) for CMCD values after stimulation of the intact hemisphere for biceps was −1.14 (95% confidence limits −1.7 to −0.5) and for threshold was −0.74 (95% confidence limits −1.06 to −0.42).

The thresholds and CMCD of the ipsilateral responses in biceps were lower than those of healthy subjects and the amplitudes were greater (see figure 4, G through L, $p << 0.01$ for all three variables). Indeed, the thresholds and CMCD for ipsilateral responses in biceps were within the normal range for age of the contralateral responses (see figure 4, J and K).

Stroke group. Contralateral responses were evoked in all subjects (see figures 2B and 4, D through F). There was a lower probability of evoking ipsilateral compared with contralateral responses (biceps, ipsilateral 50%; contralateral 100%; $\chi^2 = 8.0$, $p < 0.005$; FDI, stroke ipsilateral 13%, contralateral 100%; $\chi^2 = 49$, $p < 0.0001$; see figure 4, A through C versus figure 4, D through F). Ipsilateral responses had higher thresholds, longer CMCD, and smaller amplitudes than contralateral responses (see figure 4, D through F, $p < 0.001$ for all three variables). The probability of evoking ipsilateral responses and their thresholds, CMCD, and amplitude ratios were not significantly different from those of healthy adults (see figure 4, J and K, and figure 4, A through C, versus figure 4, D through F).

Cross-correlation analysis of the EMG of homologous muscles in the upper limb during spontaneous cocontraction. Peaks were not observed in the multiunit cross-correlograms of the EMG of right and left biceps in neonates (see figure 1B). A significant central peak in the cross-correlogram of FDI only was observed in the one subject with spastic hemiplegic cerebral palsy who showed significant mirror movements. The peak was centered at a time lag of −2 msec (see figure 2D) and had a duration of 14 msec and a synchronization index of 1.3.[18] Cross-correlograms of Pmaj and biceps in the same subject did not reveal peaks in the cross-correlogram (see figure 2D). No peaks were observed in the cross-correlograms of the other subjects with hemiplegic cerebral palsy.

Discussion. This is the first report of ipsilateral motor-evoked responses after TMS in neonates and children aged less than 3 years. In the neonates, ipsilateral responses are evoked with similar thresholds and amplitudes but are *shorter* CMCD than contralateral responses. We previously demonstrated that contralateral responses after TMS in neonates arise from direct contralateral corticomotoneuronal projections.[10] The new observations, therefore, demonstrate that direct ipsilateral corticomotoneuronal projections are also present in the neonate. Ipsilateral corticomotoneuronal projections have a shorter minimum pathway length than contralateral, because the majority do not cross the midline before descending to the spinal cord.[19,20] Assuming similar maximum axonal conduction velocities in ipsilateral and contralateral projections, a shorter conduction pathway would explain the earlier onset latencies of ipsilateral responses.

Several arguments exclude significant stimulus spread that directly excites the contralateral cortex as the origin of the ipsilateral responses. First, to control for stimulus spread we attempted to evoke responses from midline stimulation, because this would result in greater direct spread of the stimulus to the contralateral cortex than more lateral stimulation of the ipsilateral cortex. In the majority of neonates (and all other subjects), such midline stimulation failed to evoke responses, but where responses were evoked they occurred infrequently and had significantly delayed onset latencies (see figure 3). Midline responses are thus likely to have arisen from indirect activation of the motor cortex from intracortical neuronal connections rather than from direct spread of the stimulus to the motor cortex.[21] Furthermore, within individual subjects ipsilateral and contralateral responses had different onset latencies. Simultaneous activation of both motor cortices by stimulus spread would lead to ipsilateral and contralateral responses with the same onset latency. Finally, ipsilateral responses were observed after stimulation of the intact cerebral hemisphere in two subjects with stroke and seven with hemiplegic cerebral palsy, when direct stimulation of the lesioned hemisphere with stimulus intensities up to 2.5 times higher failed to evoke either contralateral or ipsilateral responses. Ipsilateral responses have also been recorded previously in subjects who have had a hemispherectomy.[5]

Another issue to be considered is the possibility that TMS in neonates excites both right and left corticospinal tracts deep to the cortex, where the projections lie close together (for example at the decussation), or, alternatively, directly excites ipsilateral brainstem descending pathways. This is improbable because TMS has been shown to excite corticospinal axons within the cortex both in humans and monkeys.[13,14,22-25] The latency of the volley evoked by TMS, recorded on the surface of the cord in both monkeys and humans[13,14,25] and from action potentials in single corticospinal axons in monkeys,[14] does not change with increasing stimulus intensity up to 100% power, demonstrating that there is little centrifugal shift in the site of activation even with high stimulus intensities. Finally, the spinal cord volley evoked by TMS in Macaque monkeys can be *completely* collided by appropriately timed microelectrode stimulation of the medullary pyramid, indicating not only that the volley arises from activation of corticospinal axons, but also that it does not involve a significant component from direct or indirect excitation of descending brainstem motor pathways.[13] The observations in the Macaque monkey are particularly relevant to newborn humans, because

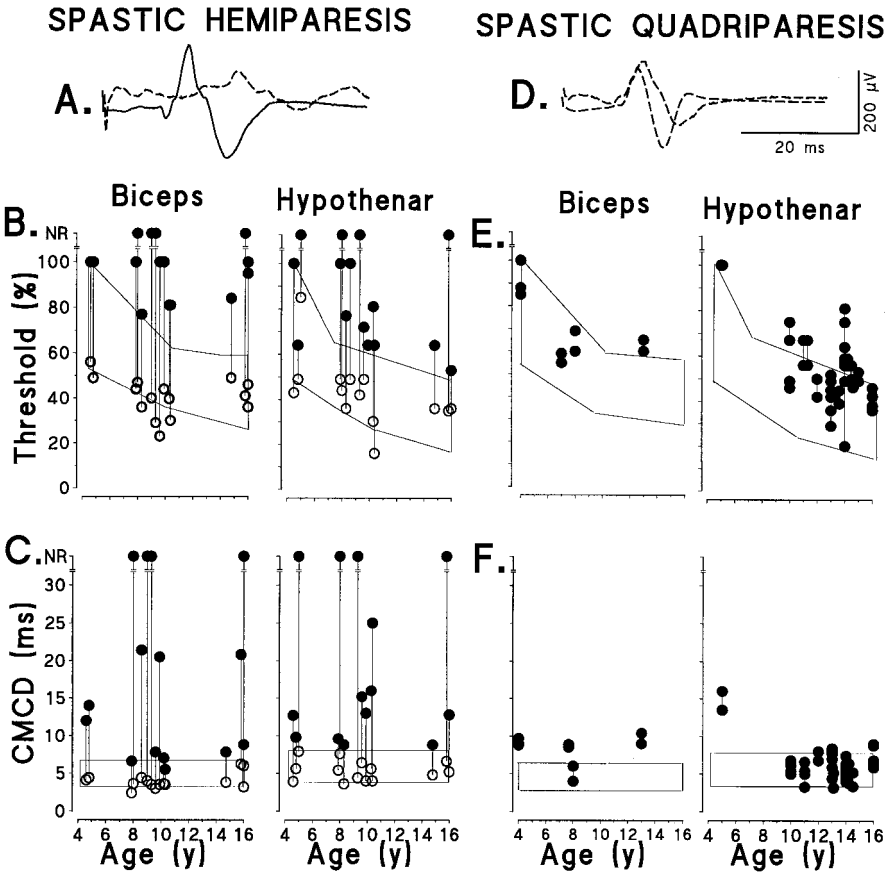

Figure 5. (A) and (D) Contralateral responses evoked in biceps after TMS of the intact (continuous line) and the lesioned (dashed line) motor cortices in (A) a subject with spastic hemiplegic cerebral palsy and (D) the left and right motor cortices in a subject with spastic quadriplegic cerebral palsy. TMS was applied at the start of each trace.In the graphs (B, C, E and F), the vertical lines join data from stimulation of each motor cortex in the same subject. Filled circles represent stimulation of lesioned cortices and open of the intact cortex. The boxed areas represent the ± 2SD ranges for age obtained in 372 healthy subjects.[9] (B and E) Thresholds in subjects with spastic hemiplegic and quadriplegic cerebral palsy respectively. Threshold is expressed as % of maximum power delivered by the stimulator. (C and F) CMCD in subjects with spastic hemiplegic and quadriplegic cerebral palsy, respectively. NR = no response. Adapted from Eyre et al.[69]

the size of the adult Macaque monkey brain is smaller than that of a full-term neonate.[10]

Two lines of evidence imply that direct ipsilateral corticomotoneuronal projections are also present in adults. First we observed ipsilateral responses in Pmaj occurring 0.8 msec *before* contralateral responses in one adult subject and within less than 1 msec later in four additional subjects. Ipsilateral responses in deltoid have also been reported, which occurred simultaneously with, or slightly before, contralateral responses.[26] Such observations would be unlikely if there was an additional synaptic delay in the ipsilateral compared with the contralateral projection. Second, TMS evokes ipsilateral responses in hand muscles,[26-28] and there is no evidence for oligosynaptic corticospinal projections to small muscles of the hand in higher primates, including humans.[29-36]

It has been argued that ipsilateral responses arise in adult subjects from the oligosynaptic "corticorecticulospinal" pathway.[28] This conclusion was based on the observation that turning the head toward the muscle being stimulated facilitated ipsilateral but not contralateral responses, because the latency of ipsilateral responses decreased, whereas that of contralateral responses did not. The authors argue that such apparent dissociation of the effect of head turning indicates that separate pathways mediate ipsilateral and contralateral responses and that ipsilateral responses cannot be mediated by the corticospinal tract. However, the *magnitude* of both ipsilateral and contralateral responses increased significantly, showing facilitation of both responses with head turning, thus casting doubt on the conclusion that there was dissociation of the effect. A possible alternative explanation is that with the head in the midline position, ipsilateral responses arose from indirect activation of ipsilateral corticospinal axons and contralateral responses from direct activation. Because turning the head toward the muscle stimulated facilitated the excitability of both responses, this facilitation could have led to direct excitation of the ipsilateral corticospinal pathway.[24,37]

Although ipsilateral responses in neonates had similar thresholds and amplitudes and shorter onset latencies, they occurred significantly less frequently than contralateral responses (see figure 3D), indicating that differences in the projections exist at birth. Subsequently, we observed rapid differential development of ipsilateral and contralateral responses, so that by 15 months ipsilateral responses, as well as occurring less frequently, were also significantly smaller, had longer CMCD, and had higher thresholds than contralateral responses (see figures 1 and 4, J and K).

In the current study we observed a lower threshold for evoking contralateral responses at all ages than in our previous studies (see figures 1D and 4J versus figure 5, B and E). The only difference in methods between our previous and current studies was the stimulating coil used. Previous studies used a 9 cm diameter round coil, whereas in the current study a figure of eight was used. The peak magni-

tude of the magnetic field generated by the figure of eight coil is greater than that of a round coil, provided that the coils are driven with the same energy.[38] The lower threshold for evoking contralateral responses using the figure of eight coil occurred because we defined threshold in terms of the energy delivered to the coil.

Using the round coil, we previously observed that thresholds for exciting contralateral responses are high in the newborn and decrease progressively with age, whereas in the current study the threshold increased postnatally to peak at 3 months before progressively decreasing (see figure 1D and figure 4J). At suprathreshold levels of stimulation, both the round and the figure of eight coils evoke similar volleys in the corticospinal tract.[25,39] It is unlikely, therefore, that the rise in threshold over the first 3 postnatal months observed using the figure of eight coil results from developmental changes in corticospinal synaptic transmission or α-motoneurone excitability, because a similar rise in threshold would be expected using the round coil. TMS using both coils excites axons within the cortex rather than the cortical neurones.[39,40] If the postnatal increase in TMS threshold reflected a developmental increase in the threshold of axons or their ability to excite transynaptically corticospinal neurones, then once again one would expect to observe a similar rise in threshold using the round coil. The figure of eight coil was chosen for the current study because the magnetic field it generates is focused under its central crossover point, thereby reducing the probability of stimulus spread to the opposite cortex. The 9 cm round coil generates a magnetic field over a greater volume, and also has a less pronounced fall-off in magnetic field intensity with distance from the coil.[41] The critical field strength for exciting axons is generated over a much smaller volume using the figure of eight coil than the round coil. The figure of eight coil will, therefore, be more sensitive to postnatal reductions in the number of cortical axons within the volume of critical field strength. The increase in TMS threshold observed only with the focal figure of eight coil would be consistent with a substantial postnatal reduction in corticospinal axonal number.

In the monkey, a threefold reduction in the number of cortical neurones projecting to the spinal cord occurs postnatally,[42] and there are also substantial reductions in axonal number in cortico-cortical connections[43] and in all other axonal projections studied[44] (e.g., optic tract, callosal projections,[45] thalamocortical projections,[46] and reticulogeniculate pathway).[47,48] Surprisingly, no evidence was found for a postnatal reduction in corticospinal *synapses* in the cervical spinal cord postnatally in Macaque monkeys.[49,50] This observation, however, is likely to reflect the methodology used because anterograde labeling of axons projecting from the hand area of the primary motor cortex was used. Such focal anterograde labeling would not detect projection and withdrawal of corticospinal axons and synapses from other areas of the cortex, including other areas of the motor cortex. It is from these other areas that the majority of supernumerary axons arise both in subprimate mammals[51] and in the Macaque monkey.[42] Furthermore, elimination of supernumerary synapses occurs in conjunction with the proliferation of synapses from the subset of axons that are maintained, and it is these axons which are labeled by anterograde tracers. Thus net increases in synaptic density have been observed during significant axonal withdrawal in other primate systems.[45,52]

The differential development of the ipsilateral responses observed in the current study, which become progressively smaller and developed higher thresholds and longer CMCD than contralateral responses, imply a greater withdrawal of ipsilateral corticomotoneuronal projections than contralateral, particularly in the first 15 to 18 months after birth (see figures 1 and 4, J through L). The small and late ipsilateral responses observed in older children and adults are consistent with the persistence of a small ipsilateral corticomotoneuronal projection, with slower conducting axons than contralateral projections. This is supported by anatomic studies in humans and monkeys that demonstrate that the corticospinal tract has approximately 8 to 15% of uncrossed axons.[20,19,49] These ipsilaterally projecting axons have been shown to arise from similar areas of the cortex and to have a similar pattern of spinal innervation to the contralateral projection.[19,20,53]

We observed low threshold, large amplitude, and short onset latency ipsilateral responses in subjects with spastic hemiplegic cerebral palsy. Such responses did not occur in subjects with stroke who had acquired unilateral cortical lesions in adulthood, establishing that fast ipsilateral responses are not unmasked by such lesions. These observations replicate previous findings in subjects with congenital hemiplegia[5,6,8] and adults with stroke.[54] The new observation is that peaks in the cross-correlations of the EMG of homologous upper limb muscles during periods of voluntary co-contraction were not observed in the hemiplegic cerebral palsy group, except for the one subject with mirror movements. In this subject, a peak was observed in the cross-correlogram of FDI only and not in that of Pmaj or biceps (see figure 2D). Thus, we could find no evidence of significant common drive to homologous motoneuronal pools on opposite sides of the spinal cord, as would be expected if there was branching of the contralateral corticospinal projection from intact hemisphere giving rise to bilateral corticomotoneuronal innervation. Subjects with Kallmans syndrome (who have mirror movements as part of the syndrome) similarly have short latency, low threshold ipsilateral responses to TMS in the absence of peaks in the cross-correlogram of their EMG.[55] Although Carr et al.[6] found peaks in the cross-correlograms of EMG from homologous hand muscles of subjects with spastic hemiplegic cerebral palsy and mirror movements, some of their hemiplegic subjects without mirror

movements also had short onset, low threshold ipsilateral responses in the absence of such peaks. Mirror movements and the broad peak in the cross-correlograms observed by Carr et al.[6] and by us (see figure 2D) would be consistent with intracortical synchronization of contralaterally and ipsilaterally corticospinal neurones projecting from similar areas of the intact hemisphere.[1,55-59]

Two further observations in the current study indicate direct ipsilateral corticomotoneuronal projections from the intact hemisphere. First, ipsilateral responses were observed in subjects with hemiplegic cerebral palsy that had significantly lower thresholds and shorter onset latencies than contralateral responses. Second, ipsilateral responses, particularly in Pmaj, were frequently larger in amplitude than contralateral, implying a greater ipsilateral than contralateral projection (see figures 2C and 4I). Finally, the presence of an unbranched ipsilateral projection from the intact motor cortex has been recently been demonstrated in a subject with congenital hemiplegia.[8]

TMS of the intact cortex evoked contralateral responses which, although within the normal range for age, were abnormally clustered toward short CMCD and low thresholds. Together these findings imply an increase in the number of fast conducting ipsilateral and contralateral corticospinal axons from the intact hemisphere after perinatal unilateral brain damage involving the corticospinal system. This conclusion is supported by direct measurement of corticospinal axonal number in the bulbar pyramid obtained at postmortem, which demonstrate significant increases in the numbers of corticospinal axons, particularly larger diameter axons, projecting from the intact hemisphere in adult subjects with spastic hemiplegic cerebral palsy, in comparison with healthy subjects and those with lesions acquired in adulthood.[60,61] Similarly, MRI studies of subjects with early unilateral brain damage demonstrate an increased size of the corticospinal projection from[62] and a shift of cortical sensorimotor functions to the intact hemisphere.[7] Finally, the short-onset ipsilateral responses observed in subjects with Kallmans syndrome are associated with significant hyperplasia of the corticospinal tract.[55] These observations and the data of the current study support persistence of ipsilateral and contralateral corticospinal projections from the intact hemisphere, which would normally have been withdrawn, after unilateral perinatal lesions, consistent with observations made in other mammalian species.[1]

Three studies in monkeys have failed to reveal comparable plasticity of corticospinal development; however, none has replicated the appropriate circumstances in which plasticity has been documented to occur in sub-primate mammals and in humans. The lesions were either induced too late in development[63] or were too focal[64] because reorganization of the ipsilateral projection from intact hemisphere has only been observed after early and extensive lesions. In the final study, hemisection of the cervical spinal cord was performed, thus the lesions were below the pyramidal decussation and involved projections from both hemispheres.[65]

In the kitten, it has been demonstrated that unilateral inhibition of the motor cortex causes exuberant corticospinal projections from the uninhibited cortex to be maintained, at the expense of those from the inhibited cortex, which become much reduced.[66] The reduction in corticospinal projection from the inhibited cortex was caused by interhemispheric competition between the corticospinal projections and not by activity blockade per se, because in a subsequent study bilateral inhibition of the motor cortices, which eliminated interhemispheric competition, led to qualitatively normal projections from both hemispheres.[67] Competitive activity-dependent refinement of bilateral corticospinal projections demonstrates parallels between the mechanisms governing early postnatal development of the corticospinal system and that of the visual system. Monocular retinal activity blockade, for example, reduces the thalamic territory occupied by silenced retino-geniculate terminals and expands the active terminal's territory. By contrast, binocular activity blockade, which similarly eliminates interocular competition, does not.[68]

Twelve years ago in our initial studies of corticospinal function using TMS, we made observations which we now realize support the relevance of these observations to corticospinal development in humans (see figure 5).[69] The same methods were used as in the current study, except that the stimulating coil was round (9 cm diameter). We compared the contralateral corticospinal projections in subjects with severe spastic hemiplegic and quadriplegic cerebral palsy who had similarly severe pathology of hand and upper limb movement control. In subjects with spastic hemiplegic cerebral palsy, TMS of the lesioned cortex either failed to evoke responses or evoked responses with abnormally high thresholds and prolonged CMCD (see figure 5, A through C). In contrast, responses with relatively short CMCD and low thresholds were evoked from the intact hemisphere, findings that we have now replicated in the current study. In subjects with spastic quadriparesis, however, responses from both hemispheres lay predominantly within the normal range for both CMCD and threshold (see figure 5, D through F). These observations are consistent with subjects with unilateral perinatal lesions having a significant reduction in the corticospinal projection from lesioned hemisphere and an increased projection from the intact hemisphere, whereas those with bilateral perinatal lesions maintain qualitatively normal projections from both hemispheres.

The findings in the kitten[66,67] and our own studies in humans suggest that the degree of abnormality of the corticospinal projection from the lesioned hemisphere may not reflect simply the death of corticospinal neurones from the initial insult, but also the

competitive displacement of surviving corticospinal projections by axons from the intact hemisphere. Progressive displacement of surviving corticospinal projections from the intact hemisphere with development may provide an explanation for the clinical observation that signs of hemiplegia are often not established in some children until well into the second year of life.[70] Such changes would be analogous to the progressive development of amblyopia in the visual system in a child with strabismus. If competitive displacement of intact corticospinal projections during development after unilateral perinatal lesions is substantiated by further studies, this is likely to have a major impact on rehabilitation, which could then be targeted to increase the competitive advantage of surviving corticospinal projections from the lesioned cortex.

Finally, during a critical period in early development synaptic inputs from descending motor pathways shape spinal motor center development.[10] After perinatal lesions to the corticospinal system there is significant secondary disruption of spinal motor center development.[71-74] Rehabilitative strategies that maintain cortical input to spinal motor centers are likely, therefore, also to reduce disability by facilitating normal development of spinal reflex pathways.

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