The Corticospinal System: From Development to Motor Control

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The corticospinal system is the principal motor system for controlling movements that require the greatest skill and flexibility. It is the last motor system to develop. The pattern of termination of corticospinal axons, as they grow into the spinal gray matter, bears little resemblance to the pattern later in development and in maturity. Refinement of corticospinal terminations occurs during a protracted postnatal period and includes both elimination of transient terminations and growth to new targets. This refinement is driven by neural activity in the motor cortical areas and by limb motor experience. Developing corticospinal terminals compete with each other for synaptic space on spinal neurons. More active terminals are more competitive and are able to secure more synaptic space than their less active counterparts. Corticospinal terminals can activate spinal neurons from very early in development. The importance of this early synaptic activity appears to be more for refining corticospinal connections than for transmitting signals to spinal motor circuits for movement control. The motor control functions of the corticospinal system are not expressed until development of connectional specificity with spinal cord neurons, a strong capacity for corticospinal synapses to facilitate spinal motor circuits, and the formation of the cortical motor map. NEUROSCIENTIST 11(2):161–173, 2005. DOI: 10.1177/1073858404270843

The timing of motor development in different species, compared with development of other bodily functions, is remarkably diverse. Some animal species are born with extraordinary capabilities. Consider the wildebeest, an animal with precocious motor skills. It is able to maintain a quadrupedal posture within moments after birth and can run with the herd soon thereafter. By contrast, many mammals—including rats, cats, and humans—are born with the capacity only to express motor behaviors that are necessary for survival, such as respiration and feeding-related behaviors (Muir 2000). Rats develop mature motor skills during the first month, and cats during the first 2 to 3 months. Human motor development is charted in years. Given the capacity for complex inter-joint control in precocious species at birth, late motor development in altricial species is not an obligatory developmental constraint.

Motor behaviors in maturity are produced by the integrated actions of diverse brain regions together with the various motor pathways that converge on spinal motor centers. During development, this is probably no differ-ent. Precocious species must have well-developed motor systems, with pathways linking supraspinal motor centers and the spinal cord. The complementary idea that the motor systems of altricial species are not developed is only partially true: The brainstem motor systems are well developed by birth, but the corticospinal system is not (Martin and others 1980; Kudo and others 1993). In maturity, the corticospinal system confers the capacity for the most adaptive and skillful motor functions, especially those of the forelimb during reaching and manipulation (Porter and Lemon 1993). During early corticospinal system development, reaching and manipulative behaviors are either not expressed (Lawrence and Hopkins 1976; Levine and others 1980; Porter and Lemon 1993; Westerga and Gramsbergen 1993; Galea and Darian-Smith 1995; Muir 2000) or have so few of the mature characteristics that they are unlikely to be the same behaviors later in development and in maturity (Bower and others 1970; Hofsten 1982; Konczak and others 1995; van der Meer and others 1995).

Although the emergence of motor behavior undoubtedly reflects maturation of diverse cognitive, sensory, and motor systems, the correlation between late motor development and late development of the corticospinal system is significant. As the corticospinal system matures, adaptive motor behaviors begin to be expressed (Lawrence and Hopkins 1976; Martin and Bateson 1985), and damage to this system severely impairs adaptive control (Armand and Kably 1993). Development of

Box 1: Organization of the Mature Corticospinal System

The corticospinal system connects the frontal and anterior parietal lobes with the spinal gray matter. Early in development, corticospinal neurons are distributed throughout much of the frontal and parietal lobes, and parts of the occipital and temporal lobes, but their distribution is later restricted to the posterior frontal and anterior parietal lobes (see figure). This developmental restriction in corticospinal neuron distribution is not due to widespread cell death but mostly to elimination of axon branches projecting to the spinal cord (Oudega and others 1994).

The corticospinal tract courses from the cortex through the deep white matter to the brain stem. Most axons of the corticospinal tract decussate from one side to the other in the lower brain stem (termed the *pyramidal decussation*; shown in figure) and descend in the contralateral white matter of the cord, as the lateral corticospinal tract. A small percentage of axons do not decussate in the pyramid (not shown in figure) and descend as the ventral corticospinal tract. In addition to the corticospinal tract, the corticospinal system contains indirect paths that project first to brain stem motor nuclei and from there to the spinal cord.

The spinal gray matter is the target of the corticospinal tract. It is composed of the dorsal horn, intermediate zone, and ventral horn. There is an alternative division, the 10 laminae of Rexed, which are defined on the basis of the density and other morphological characteristics of neurons. The borders of the various laminae are lightly shaded in the figure. The corticospinal projections from the primary motor and premotor cortical areas (light and dark blue) are to the motor regions of the spinal cord—the deeper laminae of the dorsal horn, the intermediate zone, and the ventral horn. These termination fields are colored blue in the figure. Monosynaptic projections to motoneurons in the ventral horn (lamina 9) are present in humans, apes, and some monkey species (Kuypers 1981). The origin of this projection is mostly the primary motor cortex. Cats have only disynaptic projections to motoneurons. The corticospinal system also projects from the somatic sensory cortex to somatic sensory processing centers in the dorsal horn and brain stem for regulating proprioceptive information, which corresponds to the rich array of somatic sensory information that is generated during movement. These spinal terminations are colored red. There is overlap in the somatic sensory and motor/premotor cortex projections in the deeper part of the dorsal horn.
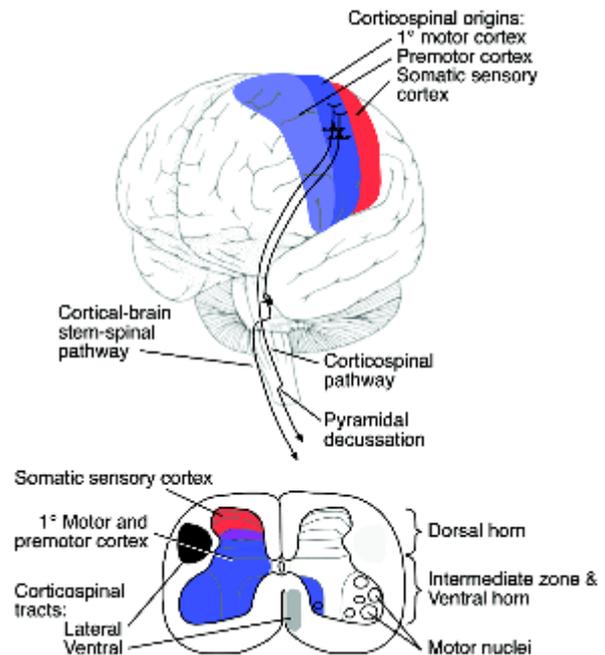
strong corticospinal connections parallels the system's ascent to become an important motor pathway (Meng and Martin 2003; Meng and others 2004) and, in humans, the principal motor system for voluntary limb control. In this review, I discuss the changes in corticospinal system anatomy and physiology that underlie the transition from development to motor control function. I take a "bottom up" approach in this review, first focusing on the protracted development of corticospinal terminations in the spinal gray matter and how the level of activity in the developing system and the animal's early motor experiences are important for achieving connectional specificity and function. Then I will show that functional development of corticospinal synapses and the cortical motor map are integrated to help establish motor control functions.

Development of the Corticospinal Projection to the Spinal Cord

Layer 5 pyramidal neurons in portions of the motor and somatic sensory cortical areas (sometimes termed *sensory-motor cortex*; see Box 1) project to the spinal cord. The growing corticospinal axons descend within specific regions of the subcortical, brain stem, and spinal white matter (see Box 1). A small contingent of "pioneer" corticospinal axons lead the way into the cord, followed later by waves of axons that further populate the corticospinal tract (Joosten and others 1987, 1989). Pathfinding is organized by tissue molecular cues that are detected by the growing primary axon (Tessier-Lavigne and Goodman 1996; Mueller 1999). Long-distance growth of the primary axon is followed by formation of side, or collateral, branches that extend into the sur-

rounding gray matter after a variable delay period (Bastermeyer and O'Leary 1996). Gray matter innervation is mediated by target-specific chemotropic factors that induce branching. In tissue explant experiments, for example, neurites from a portion of the sensory-motor cortex that will later become the forelimb area grow toward a cervical spinal explant but not to a lumbar explant (Kuang and others 1994). This indicates the importance of target-derived factors that diffuse into the local environment to attract and guide growing corticospinal axons. Recent studies of neurons in culture show that guidance cues that are attractants can become repellants by manipulating cyclic nucleotide levels within cells (Song and others 1998). Thus, the final targeting at this early stage of development depends both on the target and the internal state of the neuron. (See earlier reviews, which have focused on different aspects of early corticospinal system development [Stanfield 1992; Joosten 1997].)

The particular pattern of axon collateral branching into spinal segments constrains which spinal circuits a corticospinal neuron can engage, and therefore the neuron's functions. This level of corticospinal axon targeting is mediated by target-derived diffusible substances. Although this process is highly complex and well regulated, only coarse patterns of connectivity are achieved. Whether corticospinal neurons ultimately form functional connections with one or another segmental or propriospinal circuit, which is the basis for its motor control functions, depends on a more refined pattern of connectivity.

Development of Corticospinal Connectional Specificity

A common feature across many species is that the corticospinal termination pattern present early in development is more extensive than the one later in development and in maturity. The initial termination pattern in opossums, rats, and cats is extensive dorsoventrally (Cabana and Martin 1985; Theriault and Tatton 1989; Alisky and others 1992; Curfs and others 1994; Li and Martin 2000, 2002). In kittens (Fig. 1, *left*), cervical spinal terminations from restricted areas of the forelimb representation of the motor cortex can stretch from superficial to deep laminae, covering all but the most ventral portion of the gray matter (Li and Martin 2000). In mature cats (Fig. 1, *right*), terminations from the same motor cortex regions are much more restricted. Terminations that are eliminated later in development are often termed *transient terminations*.

Whereas most corticospinal terminations in adults are contralateral to their origin in the cortex, during development they are also extensive in the ipsilateral gray matter (Fig. 1, *left*). In the cat, for example, many corticospinal branches also cross in the spinal cord at the termination level. These axon branches are "double crossed," once in the medullary pyramid (see Box 1) and then in the cord. Most of these ipsilateral terminations
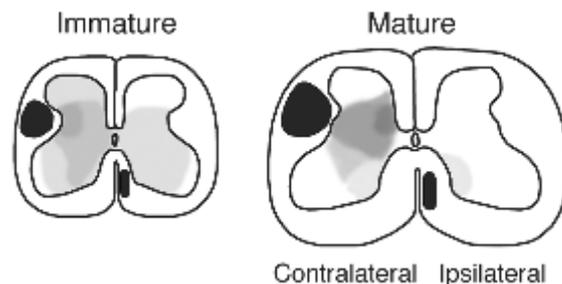

Fig. 1. Elimination of transient corticospinal terminations. The distribution of corticospinal axons is determined using an anterograde tracer that is injected into the primary motor cortex and follows the axons of the corticospinal tract, as outlined in Box 1. The density of corticospinal axon terminals is shown schematically as progressively darker shades of gray. The axons in the tracts are shaded black. The terms *contralateral* and *ipsilateral* refer to the side of the spinal cord in relation to the locations of the traced corticospinal neurons. The immature animal (*left*) has bilateral terminations, whereas the mature animal (*right*) has predominantly contralateral terminations.

are eliminated; those that persist are mostly located ventromedially (Fig. 1, *right*; see Box 1). There are also more axons in development that descend without decussating in the pyramid and terminate in the ipsilateral gray matter (Joosten and others 1992).

A set of developmentally regulated molecules, the Ephrins, and their eph receptors are important in constraining ipsilateral corticospinal terminations. Ephrin B mRNA is expressed along the midline in the developing spinal cord (Kullander and others 2001), and Ephrins, as a class of molecule, repel growing axons (O'Leary and Wilkinson 1999). Ephrin B or ephA4 knockout mice have a bilateral corticospinal termination pattern in maturity (Coonan and others 2001; Kullander and others 2001; Yokoyama and others 2001). Ephrin B or ephA4 expression may be developmentally regulated in the cord to prevent re-crossing at certain times during development or by particular corticospinal axons.

Developments of segmental corticospinal terminations in the monkey have been reported to follow a different pattern (Armand and others 1997). Anterograde tracing of corticospinal axons in infant rhesus monkeys between 4 and 5 days old shows a very restricted pattern, primarily within the contralateral dorsal horn and intermediate zone (Kuypers 1962; Armand and others 1997). Although the termination pattern is restricted at birth, it cannot be ruled out that refinement of topographically extensive connections occurred prenatally. Prenatal refinement of the corticospinal and other motor systems would also help to explain why the newborn rhesus monkey has sufficient upper body strength to cling tightly to its mother (Hinde and others 1964) and why they begin reaching at 3 to 4 weeks of age (Lawrence and Hopkins 1976). In this regard, rhesus monkeys are precocious compared with rats and cats, which are just barely able to crawl at birth. Rather than branch elimination, there is late growth of corticospinal axons into the ven-

tral horn in the monkey. Between birth and about 8 months, corticospinal axon terminals populate the lateral motor nuclei to establish corticomotoneuronal connections (Kuypers 1962; Armand and others 1997). Using transcranial magnetic stimulation (TMS) to activate corticospinal neurons in anesthetized animals, there are parallel reductions in the thresholds for evoking peripheral motor responses and increases in conduction velocity (Olivier and others 1997). As these connections develop, monkeys begin to move their fingers more independently (Lawrence and Hopkins 1976; Flament and others 1992; Galea and Darian-Smith 1995). Despite differences in topography early in development, in all species corticospinal terminals "grow into" their final termination patterns.

Understanding development of corticospinal terminations in humans is more complicated and controversial, partly because techniques to probe the system are indirect. TMS of the sensory-motor cortex is commonly used to infer anatomical connections in human studies by evoking motor responses (Amassian and others 1987; Capaday 2004). This is similar to its use in monkeys, but without corresponding tract tracing data. TMS evokes motor responses in infants, even preterm (Koh and Eyre 1988; Eyre and others 2000), but it is a more sensitive means of assessing corticospinal functional connectivity after about 1 year, when responses are more consistently evoked by stimulation (Müller and others 1992; Nezu and others 1997). Moreover, the motor thresholds decrease throughout early development and mid to late adolescence (Nezu and others 1997). The threshold reduction could be due to production of more phasic and synchronous activation of spinal motor circuits because of myelination (Yakolev and Lecours 1967) or development of spinal synapses. Recently, a provocative study by Eyre and colleagues (2001) suggested the presence of early bilateral corticospinal terminations. They reported that TMS evokes bilateral arm motor effects (both distal and proximal muscles) in both preterm and term infants. The amplitude of the ipsilateral effects diminished over the first year of life, and there was a parallel increase in amplitude of contralateral effects. If TMS activates the direct corticospinal pathway in neonates, not the cortical–brain stem–spinal cord or another path (see Box 1), this finding is similar to development of cat corticospinal terminations. The early topography of effects is similar (i.e., bilateral motor responses with TMS in humans and bilateral corticospinal terminations in cats), as is refinement from bilateral to predominantly contralateral. More important, this would also suggest a common corticospinal developmental plan across species. These early effects could be mediated, in part, by monosynaptic connections on motoneurons. Eyre and colleagues (2000) exploited the observation that during late development, high levels of GAP-43 are present in corticospinal axons, but in much lower levels in the axons of other spinal systems. They found GAP-43 immunopositive axon terminals on motoneurons in preterm human infants. However, this finding should be cautiously interpreted because the time course of GAP-43 during human development is not well understood and GAP-43 could be expressed by other developing neural systems (e.g., serotonergic; Kawasaki and others 2001).

Elimination of transient terminations is only one part of the refinement process. Corticospinal axon terminals grow fine terminal branches and synaptic boutons over a protracted period (see Box 2; Li and Martin 2001). This process begins during early development, along with axon branch elimination, and continues into the late postnatal period and possibly into maturity (Li and Martin 2001). Corticospinal terminal growth leads to formation of dense clusters of presynaptic boutons (Li and Martin 2002; Fig. 2, compare 1 month and adult, *where arrows point to clusters*).

The morphology of these terminals matches their physiology. At 1 month in the cat, corticospinal axons have a broad termination pattern and branches of individual axons are sparse and bouton density is light (Figs. 2, 3). Electrical stimulation of the pyramid, which contains all of the descending corticospinal fibers, evokes weak responses throughout the entire dorsoventral extent of the cervical gray matter (Fig. 2, *bottom left*; Meng and others 2004). The weak response (note 30 μV maximal value on the calibration scale) is because local branches are sparse and most of the boutons do not contain synaptic vesicles (Fig. 3). Boutons (i.e., axon varicosities) without synaptic vesicles may mark nascent synapses. Morphology and physiology also match well in maturity (Fig. 2, *bottom right*). With transient terminations eliminated and the presence of dense clusters of presynaptic boutons, postsynaptic responses are dorsoventrally restricted and much larger (i.e., note 700 μV scale). Moreover, after 2 months, most of the boutons contain synaptic vesicles (Meng and others 2004; Fig. 3, Normal, *right*).

Activity- and Use-Dependent Development of Corticospinal Connectional Specificity

Why are some developing corticospinal terminations maintained while others are eliminated? And why do some that are maintained develop clusters of fine axon terminals and boutons? Does this refinement reflect the playing out of a genetic developmental program or, as in sensory systems and the neuromuscular junction, does neural activity play an important role (Goodman and Shatz 1993)? In the visual system, for example, when developing thalamocortical afferents first grow into the visual cortex, they project widely and overlap with terminations from the other eye. Over the next few weeks, the intracortical width of these terminations is pruned, to form the ocular dominance columns (LeVay and others 1978). Studies have shown that the thalamocortical terminals compete for synaptic space on layer 4 neurons in the visual cortex. Terminals that are more active are more effective in this competition (Shatz 1990). Evidence points to competition for limited amounts of neurotrophic substances (Cabelli and others 1995; Shatz 1997).

Box 2: Comparative Corticospinal Development

Three corticospinal developmental stages can be identified. The first is growth of axons of cortical lamina 5 neurons to the spinal cord gray matter. This occurs during late prenatal or early postnatal development. The second stage is refinement of the gray matter terminations. This includes both elimination of transient terminations, if present, and growth to nearby targets. The major period of concurrent growth and elimination is shown by the red box. Note that local growth continues into late postnatal life. The third stage is motor control development, during which the corticospinal system's role in distal limb control and other adaptive movements becomes expressed. This period is characterized by a mature pattern of corticospinal terminals: Loss of transient terminations has occurred, and growth to local targets is well under way. The motor cortical motor map develops during this period. Myelination begins during the refinement period, which in cats is 1 month (Huttenlocher 1970; Oka and others 1985). In humans, myelination occurs by 1 to 2 years but is incomplete for several years (Yakovev and Lecours 1967). For cats and monkeys, the time course estimates shown in the figure are based on anatomical, physiological, and behavioral data. For the human, the time course is primarily based on physiological (transcranial magnetic stimulation) findings and the time course of motor signs.
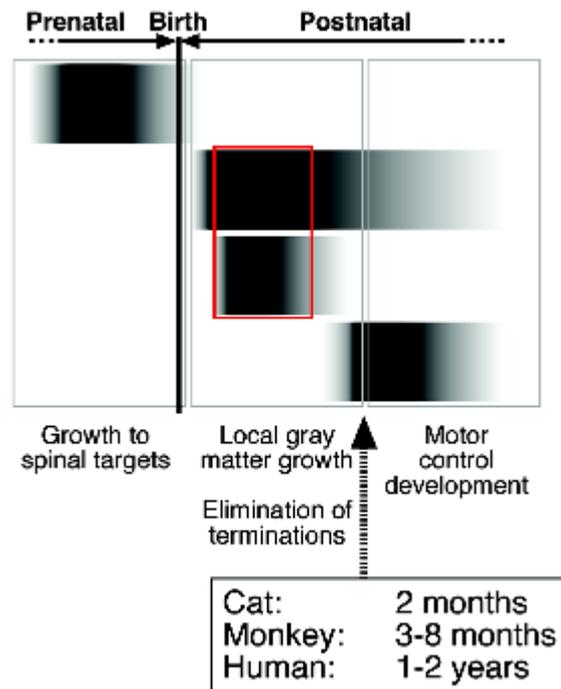
The developing corticospinal system also uses neural activity to refine the initial coarse pattern of terminations. When the corticospinal system is silenced during the postnatal refinement period (between weeks 3 and 7 in the cat), there are changes in the topographical distribution and morphology of axon terminals (Martin and others 1999). During normal development of corticospinal axons, each motor cortex projects bilaterally to the spinal gray matter at 1 month, but most ipsilateral (i.e., re-crossed) terminations are eliminated by about 2 months (Fig. 4, *left*; Theriault and Tatton 1989; Alisky and others 1992; Li and Martin 2000). If the activity of neurons in one motor cortex is blocked, by intracortical infusion of the GABA agonist Muscimol (Martin and Ghez 2001), the silenced corticospinal system fails to populate most regions of the spinal gray matter (Fig. 4, *right*, cross-hatched cortex is inactivated; yellow labeling). This impairment reflects a failure to maintain silenced axons. In contrast to the contracted topographic distribution of the silenced corticospinal system, the contralateral active system not only develops the normal contralateral projection but also maintains ipsilateral terminations in the intermediate zone and dorsal horn (Fig. 4, *right*; blue labeling). Thus, the reduction in termination space of the silenced side is balanced on that side by maintenance of ipsilateral terminations of the active sys-

tem (Martin and others 1999). These topographic changes persist into maturity. The presence of ipsilateral terminations of the active side implies that these terminals are also more competitive than the terminals of other spinal afferent systems on that side. When the motor cortices on the two sides are both silenced, a normal topographic pattern is present, although the overall density of terminations is less than expected (Martin and Lee 1999). This suggests that the topographic changes occurring during activity blockade are due to activity-dependent competition between developing corticospinal terminals and other spinal neural systems. There is evidence for interactions between the developing corticospinal and muscle afferent systems. In mature rats, more muscle afferent boutons are present in the spinal gray matter after an early postnatal lesion of the motor cortex (7 days) than after a lesion made in adults (Gibson and others 2000). Eliminating developing corticospinal terminals may have reduced competition for synaptic space in the spinal gray matter and thereby reduced pruning of muscle afferent fiber branches (Gibson and Clowry 1999).

The morphology of corticospinal axon terminals also depends on sensory-motor cortex activity (Friel and Martin 2004). Silencing corticospinal neurons results in impoverished axon terminal branching and fewer bou-
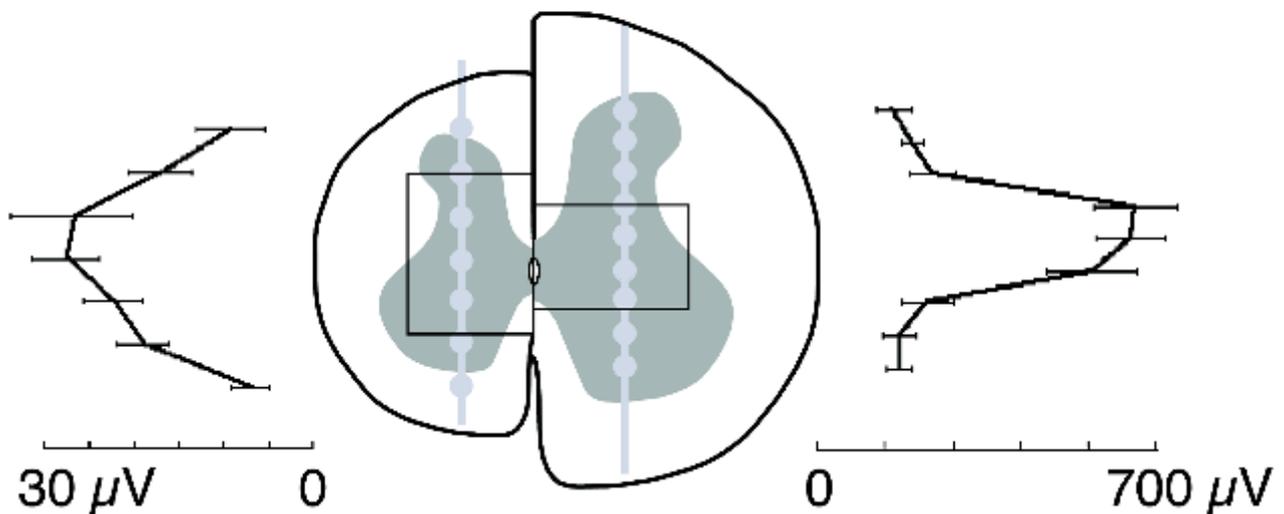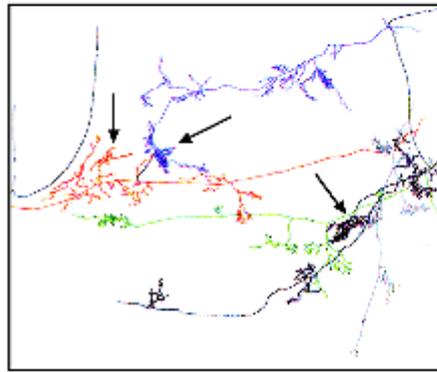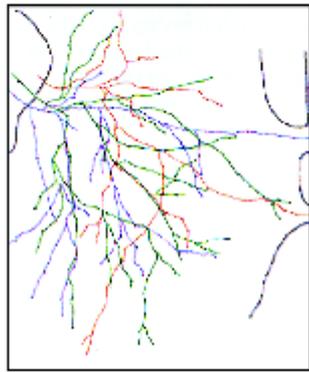
Fig. 2. Development of collateral branches of individual corticospinal axons (*top*) and postsynaptic responses (*bottom*). The branching patterns of three labeled corticospinal axons are shown. Their morphology was determined by reconstructing labeling from serial transverse spinal sections. Each axon is a different color. The dots correspond to axon varicosities, or presynaptic boutons. The immature axons (*left*; 1 month) have very extensive distributions, including ipsilateral terminations (not shown), but few fine terminal branches and boutons. By contrast, the adult axons (*right*) have a limited termination field with many fine branches and boutons. The arrows point to three clusters of fine branches and boutons. The area of reconstructed axons in the top of the figure is shown as the boxed regions in the schematic transverse spinal cord section. The changes in the amplitude of the postsynaptic responses recorded from different gray matter depths for the two ages are shown in the bottom. Approximate depths of recoding sites are shown as the dots along the schematic electrode tract in the spinal cord drawing. The graphs plot mean response amplitude ± SE. The two sides of the illustration are set up as mirror images. Axon reconstructions are adapted from Li and Martin (2002), and the response amplitude graphs are adapted from Meng and Martin (2003).

tons than normal (Fig. 3, *top*). Figure 5 shows a representative normal terminal at 2 months (*A*) and one from an animal in which the corticospinal system was silenced from weeks 5 to 7 and examined at 8 weeks (*B*). The bar graph is based on the effects of activity blockade (Friel and Martin 2004) and preventing forelimb use (Martin, Choy, and others 2004), which show similar effects. There is a drop in presynaptic bouton density; similar changes occur for axon terminal branching. These changes in morphology are persistent. Normally, there is a twofold increase in varicosity density from 2 months to maturity (Martin, Choy, and others 2004; Fig.

5, blue bars). Even though activity returned, terminations that had been silenced earlier during development show diminished growth (Fig. 5, yellow bars).

Preventing limb use (Martin, Choy, and others 2004) or cortical activity blockade (Friel and Martin 2004) during the corticospinal axon refinement period produce a remarkably similar set of morphological changes in corticospinal axon terminal development. Intramuscular injections of botulinum toxin A was used to prevent forelimb movements. Corticospinal axons failed to maintain terminations within certain gray matter fields, and there were permanent reductions in branching and varicosity
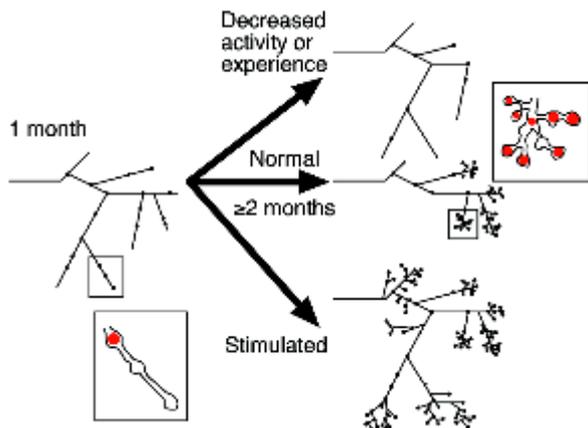
Fig. 3. Corticospinal axon remodeling. This schematic shows the normal development (*center row*) of a collateral corticospinal axon branch from long branches but with few fine terminals and boutons at 1 month, to a more restricted distribution but with many fine terminals and boutons by about 2 months. The boxed insets show the presence of axon varicosities (boutons) with or without synaptic vesicles, which are shown as a red dot that corresponds to punctate synaptophysin immunostaining. Note that only about 1/3 of the few varicosities at week 3 contain synaptic vesicles, whereas most of the varicosities contain vesicles after 7 weeks (based on Meng and others 2004). The upper path shows development after sensory-motor cortex activity blockade or after limb disuse between weeks 3 and 7 (see also Fig. 5). The lower path shows the postulated effect of corticospinal system stimulation during the same period (see also Fig. 6).

Fig. 4. Activity-dependent refinement of corticospinal axon topography. The drawings at the *top* of the figure show the frontal and anterior parietal lobes of the cat brain. The dotted outlines mark the region of the primary motor cortex. In this set of schematic drawings, the spinal terminations of the left motor cortex are traced in yellow, and for the right cortex, blue. Normal development is shown in the *left* panel. Overlapping territories in the spinal gray matter at 1 month are extensive and shown as stripes. Development after activity blockade is shown on the *right*. Activity was blocked by intracortical muscimol infusion. The silenced side terminates within a contracted region, whereas the contralateral active side terminates within the normal contralateral field but also maintains many ipsilateral terminations.

density. However, blocking limb use did not result in retention of ipsilateral terminations from the used side (unpublished observations).

Animals with early cortical inactivation or limb disuse showed permanent impairments in skilled forelimb movements during prehension (Martin and others 2000; Martin, Choy, and others 2004). For both activity and use blockade, animals lost the ability to produce a skilled distal movement during prehension (coordinated digit flexion and forearm supination during grasping). After activity blockade, an additional defect was present: the animals systematically overreached targets (Martin and others 2000). This was shown to reflect an impairment in the spatial planning of movements (Meng and others 2000). Although not yet explored, this difference in motor signs after activity blockade and preventing limb use likely reflect differences in circuit development after the treatment.

Activity blockade and limb disuse result in a loss of corticospinal terminal postsynaptic space. Our finding that when a corticospinal neuron's activity is blocked during an early period it does not recoup lost connections later in development once activity returns points to a long-term consequence to a short-term manipulation. Similar to a foot race, in which a runner loses ground to a strong competitor, developing corticospinal neurons do not catch up. The prolonged period of activity dependence creates a protracted period of vulnerability for developing corticospinal axon terminals. After perinatal
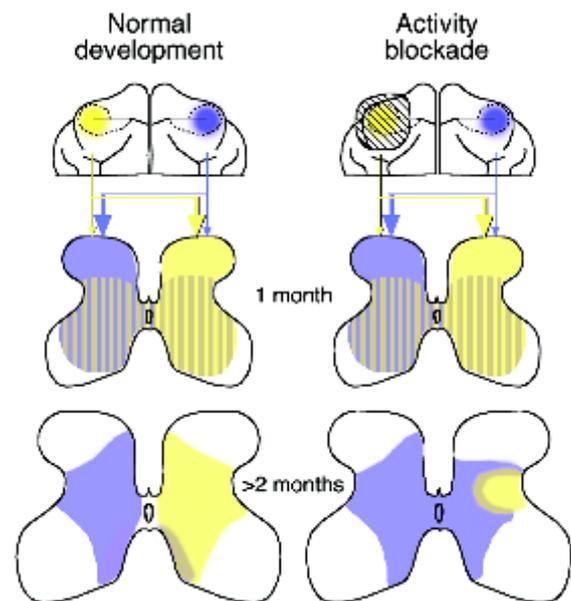
trauma in humans, it is likely that the developing corticospinal system becomes less effective in securing synaptic space. Without robust early intervention, it will remain at a permanent competitive disadvantage, producing permanent disability.

Corticospinal terminations are extraordinarily sensitive to reductions in the level and possibly the pattern of activity, but is this a bidirectional process: Does augmenting a neuron's activity enhance its competitive advantage? To answer this question, we electrically stimulated corticospinal axons in the pyramidal tract of the spinal cord (Salimi and Martin 2004). We used a burst stimulation paradigm during the refinement period (45-millisecond trains of 330 Hz stimuli) that is effective in activating spinal motor circuits in development. Animals were stimulated between weeks 5 and 8 and examined immediately after cessation of stimulation when the topographical distribution of corticospinal terminals is similar to that of the mature cat (Theriault and Tatton 1989; Alisky and others 1992). Stimulation resulted in maintenance of transient ipsilateral and ventral terminations. Figure 6 shows the distribution of corticospinal terminal label after the tracer wheat germ agglutinin conjugated to horseradish peroxidase was injected into the motor
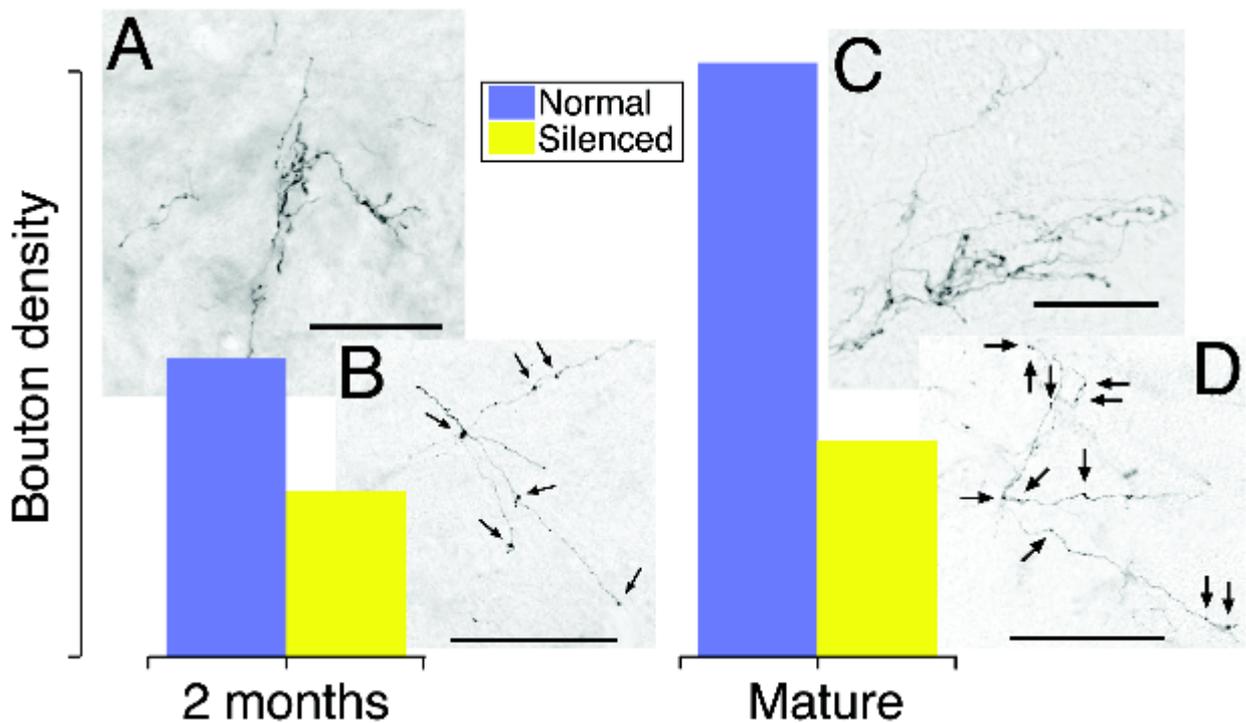
Fig. 5. Morphological changes after activity blockade or preventing limb use persist into maturity. Bar graphs are semischematic, representing data from normal animals and after either activity blockade (between weeks 5 and 7; Friel and Martin 2004) or after preventing limb use (between weeks 3 and 7; Martin, Choy, and others 2004). Data at 2 months are immediately after the treatment; data from mature animals are 4 or more weeks after treatment, in animals 13 weeks or older. *A, C,* Micrographs of normal corticospinal axon terminals at 8 and 13 weeks, respectively. *B,* Micrograph of terminal at 2 months, which is immediately after the period of activity blockade. *D,* Micrograph of terminal at 13 weeks, which is 5 weeks after the period of activity blockade. Calibrations in *A–D,* 100 μm.

cortex for a stimulated animal (*A*) and a control (*B*). The label has a golden appearance. To facilitate comparison, note the presence or absence of labeling within the yellow boxes. The age-matched control shows the contralateral label within the dorsal section only (*B1*); there is no labeling ventrally (*B2*). The intensity of labeling in this animal was particularly bright and strong. By contrast, the stimulated animal has bilateral terminations within both the dorsal section (*A1*) and the ventral section (*A2*). Similar to the active corticospinal system during unilateral activity blockade, unilateral stimulation also affects the nonstimulated side, forcing the terminations to take on a more dorsal location (Salimi and Martin 2004). These findings support the hypothesis that stimulation enhances the competitive advantage of developing corticospinal neurons. What has yet to be explored is whether the anatomical changes correlate with any enhanced behavioral capacity or if the changes can persist into maturity.

The developing corticospinal system is apt to be taking advantage of the early extensive distribution of terminations. If terminations in the transient fields prove useful for the animal, perhaps because they facilitate development of particular spinal circuits, then they may be maintained. Can activity-dependent development of the corticospinal system be harnessed to enhance the competitive advantage of the damaged corticospinal sys-

tem? Perinatal trauma or ischemia can damage the developing corticospinal system, often resulting in cerebral palsy. There are striking parallels between the pattern of movements evoked by TMS in hemiplegic cerebral palsy, which is thought to correlate with the topography of corticospinal terminations, and the laterality of corticospinal terminations after unilateral activity blockade in the cat. TMS of the less impaired side commonly produces bilateral limb motor effects (Carr and others 1993; Eyre and others 2001), whereas TMS of the impaired side does not produce effects (Carr and others 1993). This suggests the presence of bilateral terminations from the less impaired side and an impoverished projection from the affected side. This pattern is similar to the schematic shown in Figure 4 (*right*) for unilateral inactivation. Augmenting the activity of the hemiplegic corticospinal system by electrical stimulation, similar to what we have done in the cat (Salimi and Martin 2004), could enhance its competitive advantage and help maintain connections with spinal motor circuits.

Maturation of Motor Circuits in the Spinal Cord and Cortex

During early postnatal development, extensive anatomical changes occur whereby the topography and morphology of corticospinal terminals become like those in
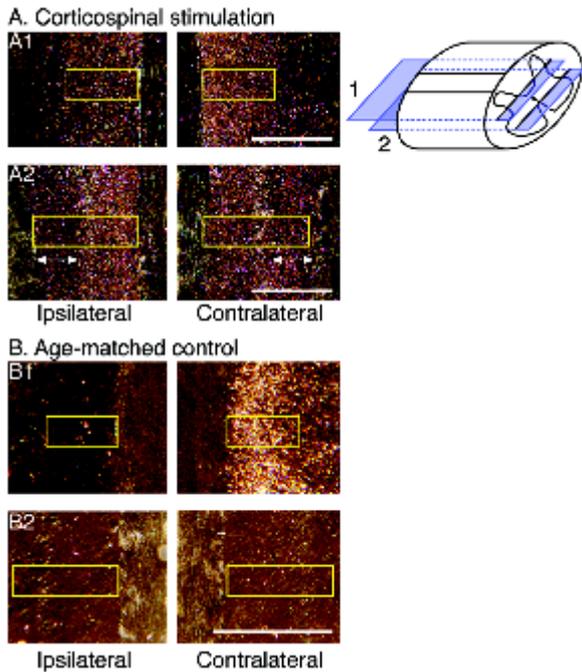
Fig. 6. Effect of corticospinal system stimulation. Polarized dark-field micrographs, in the horizontal plane, are shown for an animal that received pyramidal tract stimulation between 5 and 7 weeks (*A*) and age-matched control (*B*). The intensity of labeling in the control animal was particularly bright and strong. The micrographs in *A1* and *B1* are through the dorsal horn. The plane of section is shown in the inset, and marked 1. The micrographs in *A2* and *B2* are through the motor nuclei in the ventral horn, and the plane is marked 2 in the inset. For each pair of micrographs, the one on the right is contralateral to stimulation and the one on the left is ipsilateral. To facilitate comparison, note the presence or absence of labeling within the yellow boxes. The arrows in *A2* delineate the boundaries of the motor nuclei. Label density on the ipsilateral side is greater for the stimulated animal. Calibrations in *A*, *B* are 1 mm. Adapted from Salimi and Martin (2004).

maturity. This is also the period when there is a rapid improvement in motor skills. Although development of motor control during this period likely depends on maturation of multiple cognitive, sensory, and motor systems, the role of the corticospinal system now can be much more important. This is because of particular morphological and physiological changes of the corticospinal terminals that lead to more effective synaptic activation of spinal motor circuits. As described earlier, a much higher percentage of corticospinal terminals contain synaptic vesicles in the cat after 2 months (Fig. 3; Meng and others 2004). As more functional terminals are added after this age, there should be a larger postsynaptic response for a given descending control signal (Meng and others 2004).

In addition to added synaptic strength through more neurotransmitter release sites, the other part of the transition from corticospinal development to motor control function is the capacity for more effective temporal facilitation of descending control signals. Facilitation is a form of short-term response enhancement that is
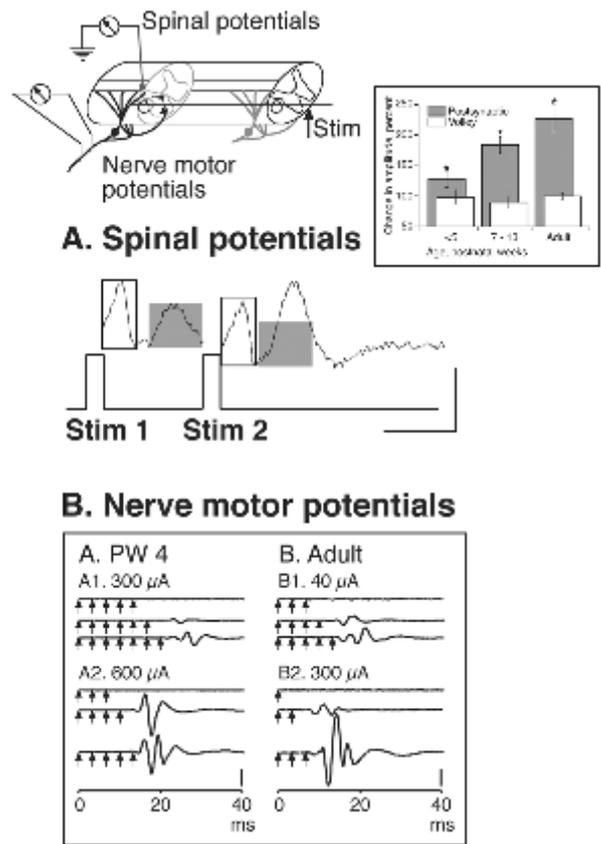

Fig. 7. Corticospinal postsynaptic response facilitation and motor facilitation. Spinal potentials (*A*) were recorded from the dorsolateral surface of the sixth cervical segment in response to a pair of pyramidal tract stimuli. The volleys and postsynaptic responses are enclosed in open and gray boxes, respectively. The size of the open and gray boxes matches the amplitude of the volley and postsynaptic potentials to the first stimulus. Note that although the volleys are the same for each stimulus, the second postsynaptic response is larger, indicating that it was facilitated. Data from all cats, at the various ages, are shown in the inset above the recordings. Bars plot the change in amplitude of the monosynaptic response. Recordings from the musculocutaneous nerve in response to multiple pyramidal tract stimuli are shown below (*B*) for a 1-month-old animal (*left*; *A*) and an adult (*right*; *B*). Each tracing shows the number of stimuli (*arrows*) and the evoked response at two different currents. PN = postnatal week. Data from Meng and others (2004).

mediated by an increase in Ca^{++} at or near release sites (Fisher and others 1997). Facilitation can be studied using double pyramidal tract stimulation (Fig. 7; Meng and others 2004): The spinal postsynaptic response evoked by the second of a pair of pyramidal tract stimuli is larger than the response evoked by the first. Pyramidal tract stimulation evokes a descending volley, corresponding to synchronous activation of corticospinal axons and a postsynaptic response (Meng and Martin 2003). In Figure 7, the volley to the first stimulus (*A*; Stim. 1) is enclosed by the open rectangle and the postsynaptic response by the gray rectangle. The second of a pair of stimuli (Stim. 2), separated by an appropriate interval (3.3 milliseconds), evokes the same volley but a

larger postsynaptic response. (The size of the open and gray boxes corresponds to the size of the volley and postsynaptic response evoked by the first stimulus.) The increment in amplitude of the postsynaptic response to the second stimulus is due to temporal facilitation (Meng and others 2004). The magnitude of this facilitation of the postsynaptic response increases as animals grow older (Fig. 7, upper bar graph inset).

Stronger postsynaptic facilitation results in stronger signal to muscle. We showed this by modifying the dual pulse stimulation paradigm to use multiple pulses, which are needed to evoke peripheral motor responses in young animals (Meng and others 2004). We recorded a motor response from an arm nerve, evoked by the stimulation (Fig. 7; see spinal inset). We characterized the pyramidal tract stimulation requirements for evoking a motor response, the current amplitude and the number of stimuli (Fig. 7B). We found that at 1 month, high-stimulus currents and large numbers of stimuli were needed to evoke responses (e.g., 6 stimuli at 300 μA was threshold; Fig. 7B). As animals grew older, responses could be evoked with fewer stimuli and lower currents (e.g., 4 stimuli at 40 μA). This shows that as the strength of CS facilitation increases with age, so too does the capacity to evoke motor responses.

Facilitation is important for corticospinal motor control functions because the structure of the motor cortical control signal requires summation of multiple spikes. In the monkey, for example, corticospinal neurons begin to increase their activity 50 to several hundreds of milliseconds before the onset of a trained arm movement (for review, e.g., Cheney and others 1991). This long lead time is surprising because action potential conduction time between the cortex and the spinal cord is less than 10 milliseconds (Fetz and Cheney 1980). This "wind-up" period is needed for temporal summation of corticospinal spikes on spinal motoneurons. The implication of stronger facilitation is that as the corticospinal system develops, the motor cortex can activate spinal motor circuits—and produce movement—with lower levels of activity.

A further step toward a strong corticospinal contribution to motor control occurs with the development of the motor representation in the primary motor cortex. The cortical motor representation, which integrates subcortical and premotor control signals to access output circuits for controlling particular joints, is first detected at 2 months in the cat (Bruce and Tatton 1980; Chakrabarty and Martin 2000). The motor map is assessed using microstimulation, whereby a microelectrode is used to excite a small population of cortical neurons. The motor responses evoked by microstimulation reflect a complex combination of activation of intracortical (Jankowska and others 1975) and spinal circuitry. Using microstimulation in developing animals and in maturity, small territories of cortex that are approximately 500 μm in diameter (Keller 1993) show a preponderance for controlling a single or small set of limb muscles (Nudo and others 1992; Martin and Ghez 1993; Chakrabarty and Martin
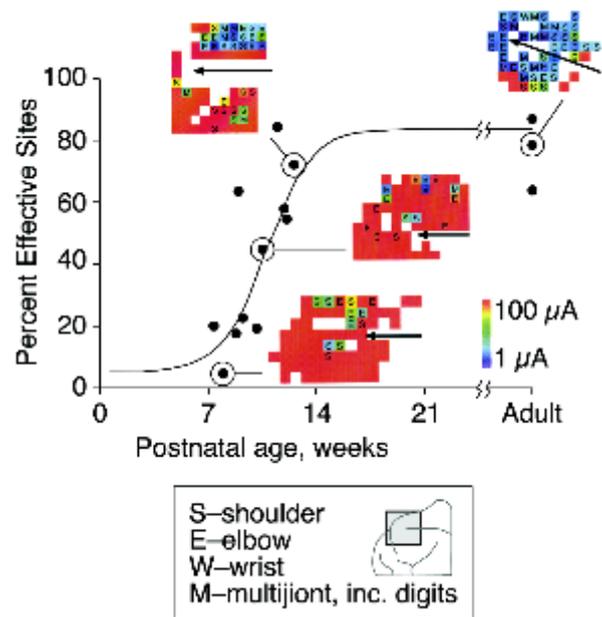

Fig. 8. Development of the cortical motor map. The graph plots the percentage of sites from which microstimulation evoked a motor response at the various ages tested. Each dot shows data from a separate animal. At four selected ages, maps of the forelimb area are shown. Color represents the amount of current needed to evoke a response. The general location of this area is indicated on the inset brain drawing, as the gray box. For the various maps, the arrows indicate the cruciate sulcus, which roughly divides the rostral and caudal forelimb areas.

2000). Using this approach, we mapped the motor cortex of anesthetized kittens at different ages to determine when the motor map develops and how the topographic organization of the motor map changes. Prior to about 2 months, motor cortex stimulation does not evoke motor responses (Bruce and Tatton 1980). During the following month, four changes in the motor representation occurred (Chakrabarty and Martin 2000; Fig. 8). First, there is an increase in the percentage of sites from which stimulation evokes a motor response (plotted in Fig. 8). Second, there is a concomitant decrease in the current threshold. This reduction can be seen on the maps of stimulation effects as a change from a preponderance of high-threshold (red) to low-threshold sites (blue). The anatomical region from where the map was obtained is shown in the inset of the cat brain. The threshold reduction suggests more efficient transduction of electrical stimuli into muscle control signals. Third, there is an elaboration of the motor map, from initially only representing proximal muscles (Fig. 8; shoulder, "S"; elbow "E") to one that represents all forelimb joints (shoulder, elbow, wrist, and multijoint "M" effects, including the digits). Fourth, as animals get older, there is a higher percentage of sites from which effects at multiple joints are produced. These multijoint sites could play a role in encoding interjoint synergies. The proximal to distal progression in motor map development is similar to the proximal to distal control strategy of human infants dur-

ing arm movement development (Berthier and others 1999). Development of the motor map has not been studied in other species.

The proximal to distal motor map development (Chakrabarty and Martin 2000) does not depend on motor experience (Martin, Engber, and Meng 2004). We have shown that the topographic characteristics of the motor map do not change when animals are trained to perform a prehension task or prevented from using one limb during the motor map development period (between 2 and 3 months). Although task performance significantly increased the number of multijoint sites, and disuse reduced the number, the effects were not sustained, diminishing to control levels over a 4-month period. This reduction back to control levels probably reflects plasticity that persists throughout the animal's life (Kleim and others 2003).

The absence of a persistent effect of early experience could be because the period of motor map development, which is during the third postnatal month in the cat, is after the period when activity or experience shapes development of the circuitry underlying its organization. Earlier activity and use manipulations, during the second month, have persistent effects on skilled motor behavior (Martin and others 2000). Development before the motor map emerges helps to establish the patterns of connections between motor cortex neurons and spinal motor circuits. The corticospinal system's capacity for adapting to changing motor demands could be embodied in these early-developing circuits, not the particular somatotopic or topographical features, which develop later (Chakrabarty and Martin 2000). Development of the patterns of horizontal intracortical connections could determine the networks that are accessed in response to particular motor control tasks. Similarly, development of the patterns of corticospinal terminations in the contralateral dorsal horn and intermediate zone would determine the kinds of segmental and propriospinal circuitry that could be activated by descending control signals. Development at this early stage would not establish the particular combination of muscles that are to be controlled. This would occur after the second month, when anatomical connectivity has stabilized (Li and Martin 2002) and as the animal's behavioral repertoire expands with greater motor planning capabilities. The specific topography of motor effects in the map could be shaped by modulating the strength of corticospinal connections within the broad termination fields of the spinal cord or within local horizontal connections in the cortex.

Conclusions

The dynamic state of the developing corticospinal system implies a different role for neural activity in this system during development, before connections have matured, and later in development and in maturity, when connections have stabilized. Corticospinal synapses are capable of activating spinal targets at very early ages, perhaps even prenatally (Eyre and others 2000; Meng

and others 2004). Activity in this system at an early age is used to shape termination topography, morphology, and possibly spinal circuits more generally. This activity, because of weak synapses and topographically inappropriate connections, does not appear to be carrying motor control signals. This may wait until corticospinal synapses can transduce supraspinal commands more effectively. Development shaped by the levels or patterns of activity underlying experience may be a way for movement parameters, such as the kinematic and dynamic features of a movement, and the sensory consequences of movement to shape the topography and morphology of corticospinal terminations and the functional organization of the system's circuitry.

The protracted period of activity and use dependence produces a protracted period of vulnerability to deviations from an optimal functional state of the motor systems. It should be possible to bring this dependence under therapeutic control when trauma to the developing nervous system threatens to impair corticospinal system function. Behavioral therapies—such as conventional physical and occupational therapy and constraint-induced therapy (Glover and others 2002; Taub and others 2004)—may be influencing the course of corticospinal system development through an activity-dependent mechanism. But these therapies are limited in their efficacy, especially when damage is severe. Direct activity manipulations—such as TMS, deep brain stimulation, or by pharmacological means—could provide a more effective way to manipulate the activity of the developing corticospinal system than behavioral therapy. This is especially the case for very early human development, when babies cannot comply with the exercise regimens set by a therapist.

What we are learning about corticospinal development is likely to apply to "re-development" after axotomy due to spinal cord injury or stroke. Indeed, much of the goal of spinal cord injury research is to reconnect the corticospinal tract, the principal path for voluntary control in humans, with spinal circuits caudal to injury. One day it may be possible to devise ways to promote corticospinal axon regeneration in patients after spinal cord injury, as has been done in animals (Huang and others 1999; Brosamle and others 2000). The rules governing refinement of corticospinal connections initially during development are also apt to apply to regenerated connections.

Activity- and motor experience–dependent development of the corticospinal system is similar to activity- and visual experience–dependent development of the visual system (Goodman and Shatz 1993). From a clinical perspective, it is well known that early visual impairments, such as with cataracts and strabismus, have a long-term consequence on sight. Our work leads to a similar conclusion for the corticospinal system and skilled movement control. However, there are important differences between development of these two systems. The period of corticospinal development appears to be longer than in vision, and vulnerability to developmental

insults extends later into postnatal life. These characteristics of corticospinal development could reflect the need to adapt to changing motor control demands as the body size and mass change throughout life. However, the protracted activity- and use-dependent development period may also provide a wider therapeutic window.

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