Descending Pathways in Motor Control

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Key Words

spinal cord, motoneuron, corticospinal, reticulospinal, tract

Abstract

Each of the descending pathways involved in motor control has a number of anatomical, molecular, pharmacological, and neuroinformatic characteristics. They are differentially involved in motor control, a process that results from operations involving the entire motor network rather than from the brain commanding the spinal cord. A given pathway can have many functional roles. This review explores to what extent descending pathways are highly conserved across species and concludes that there are actually rather widespread species differences, for example, in the transmission of information from the corticospinal tract to upper limb motoneurons. The significance of direct, corticomotoneuronal (CM) connections, which were discovered a little more than 50 years ago, is reassessed. I conclude that although these connections operate in parallel with other less direct linkages to motoneurons, CM influence is significant and may subserve some special functions including adaptive motor behaviors involving the distal extremities.

Contents

INTRODUCTION

The time is ripe for a review in this area, not only because of important new knowledge, but also because of the clinical importance attached to a fuller understanding of the role of descending pathways in motor control. There are two main areas of topical interest. In human spinal cord injury, trials are in progress in different parts of the world to test a variety of cell-based and drug-based therapeutic approaches (Ramer et al. 2005, Adams et al. 2006, Tator 2006, Courtine et al. 2007). In stroke, the physiological consequences of different types of therapy and rehabilitative approaches are being studied (Nudo 2007, Ward & Cohen 2004). For progress in these areas to continue, it is increasingly important to understand more fully the functional contribution of the different descending systems that have been injured. Whether these systems can regenerate or whether surviving systems can play compensatory roles and how these various processes can be boosted by appropriate therapy (Case & Tessier-Lavigne 2005, Deumens et al. 2005) (see **Figure 6**) are related clinical issues.

Scope and Structure

I focus very much on the comparative biology of the descending pathways and its relevance to the control of skilled hand movements. The review is structured to address the following points and issues:

- How are the descending pathways organized, and what are their defining characteristics?
- Does a descending pathway carry out single or multiple functions?
- Is the corticospinal tract a motor pathway?

- Is the organization of the descending pathways highly conserved across different mammalian species?
- What is the functional significance of direct connections with target motoneurons?

HOW ARE THE DESCENDING PATHWAYS ORGANIZED, AND WHAT ARE THEIR DEFINING CHARACTERISTICS?

Mammalian motor pathways involve a number of different descending systems, some of which are conserved from reptiles and other vertebrate species and others that have appeared much later in evolution. **Table 1** is a checklist of ten properties that characterize a descending pathway. They include key neuroanatomical features, including the origin, course, and pattern of pathway termination and also fiber number and size. We need to know much more about the molecular identity of each pathway and how this guides the pathway to cross or not to cross the midline, to find its target neurons, and to avoid others. The neuropharmacological features include the neurotransmitter and neuromodulators released at the pathway's terminals. Finally, we need to add the neuroinformatic features: the activity/information that the pathway transmits to those targets. In some cases one can inactivate or permanently lesion a pathway in a selective manner that allows additional insight into function.

Unfortunately, a completed checklist of all these features is still not available for any of the major mammalian descending pathways. We now have advanced anatomical details for many of them, but the functional roles of each pathway and how they relate to these anatomical features are still unresolved. In particular, we lack evidence in the awake animal or human volunteer as to the nature of the information that these different pathways transmit to their spinal targets. For the generation of purposeful movements, target interneurons and motoneurons must integrate this information with that from other descending pathways and propriospinal and segmental inputs.

Mechanisms controlling features such as firing threshold, synaptic gain, and possible bistable properties could all play a major part in this integrative response (Hultborn et al. 2004). We need to understand that the descending pathways function as part of a large network rather than as separate controllers of the spinal cord. As Edgerton wrote, "the spinal cord functions as part of the brain, not as its servant." Descending pathways do not simply telegraph commands for movement to the spinal apparatus; hence we should abandon the use of terms such as "upper motoneuron" and "lower motoneuron," terms of undoubted convenience in the domain of clinical neurology but with

Table 1 Ten characteristics of a descending pathway

1	Origin	Location of cells of origin of the pathway
2	Synaptic input	Nature of the major inputs to these cells of origin
3	Fiber number and size	Numbers of fibers making up the pathway, and distribution of fiber diameters within the pathway
4	Course	Trajectory followed by fibers belonging to the pathway
5	Target/termination	Location and type of interneurons and motoneurons etc. receiving terminations from the pathway: defined both by level within the spinal cord and lamina within the gray matter
6	Collaterals	Other supraspinal targets innervated by axon collaterals from the same pathway
7	Molecular identity	Characteristic surface and other molecules important for axon guidance, target finding and synaptogenesis
8	Transmitter(s) and neuromodulators	Transmitters employed at synaptic and presynaptic targets of the descending pathway
9	Activity/information transmission	Timing, pattern and type of activity exhibited by neurons contributing to the pathway
10	Lesion/inactivation	Effects on behavior

IZ: intermediate zone of the spinal cord gray matter

no modern-day neuroanatomical or neuroscientific justification.

Grouping Descending Pathways According to Their Spinal Targets

Hans Kuypers's (1925–1989) major contributions to our understanding of the neuroanatomy of the descending pathways (see Kuypers 1981) have a continuing influence in the field. He worked first with silver degeneration methods, then with retrograde and anterograde labeling using radiolabeling, fluorescent, and other tracers, and finally viral transneuronal markers (Kuypers & Ugolini 1990).

Kuypers' study of descending pathways convinced him that the key to understanding their function was to examine their termination pattern within the spinal gray matter: to define the address to which descending activity is sent (Kuypers & Brinkman 1970). Using this approach, Kuypers identified three groups of brainstem pathways.

Group A: ventromedial brainstem pathways. These include the interstitiospinal and tectospinal tracts arising from the midbrain, the lateral and medial vestibulospinal tracts (Sugiuchi et al. 2004), and the reticulospinal and bulbospinal projections arising from the pontine and medullary reticular formation (Matsuyama et al. 1997, 1999; brainstem areas colored green on the right side of **Figure 1**). These pathways descend in the ventral and ventrolateral funiculi of the spinal cord and have characteristic terminations in Rexed lamina VII and VIII, i.e., the ventromedial part of the intermediate zone (IZ), with many axons terminating bilaterally (region colored green in the spinal cord, **Figure 1**). This region of the IZ gives rise to long propriospinal neurons whose bilateral projections link widely separated parts of the spinal cord, including the cervical and lumbar enlargements. Kuypers considered this group of pathways as a bilateral postural control system for head, neck, trunk, and proximal limb movements (Lawrence & Kuypers 1968b, Kuypers 1981). An important subdivision of this group includes those involved in the control of respiration (Monteau & Hilaire 1991, Boers et al. 2005, de Troyer et al. 2005).

Group B: dorsolateral brainstem pathways. These include the rubrospinal tract arising from the magnocellular red nucleus (brainstem area and fibers colored red on the right side of **Figure 1**) (Kennedy 1990, Muir & Whishaw 2000, Kuchler et al. 2002) and the pontospinal tract (arising from the ventrolateral pontine tegmentum); they descend contralaterally in the dorsolateral funiculus. They are characterized by their pattern of termination in the dorsal and lateral regions of the IZ (region colored red in the spinal cord, **Figure 1**); this region in turn gives rise mostly to short propriospinal neurons and has more local, mainly unilateral projections. Kuypers considered this group of pathways to provide additional capacity for flexion-biased movements involving more distal limb segments, the elbow and wrist.

Emotional motor system. A number of other pathways influence motor and other functions at the spinal level. Holstege (1998) grouped these together as the 'emotional motor system'. A medial component comprises a diffuse system of pathways originating from the lower brainstem (raphespinal tract; Mason 1997), the ventromedial medullary tegmentum, the locus coeruleus, and the subcoeruleus (Tanaka et al. 1997). These fibers terminate widely at all spinal levels in the dorsal horn and among autonomic and somatic motoneuronal cell groups. Transmitters and neuromodulators in these pathways include serotonin (5-HT) and noradrenaline; the 5-HT pathways exert a major level-setting influence on spinal reflexes and motoneuronal membrane properties and excitability (Heckman & Lee 1999).

A second, lateral component originates from cell groups in the mid- and forebrain, which are involved in a number of specific motor activities, including defensive reactions, pupil

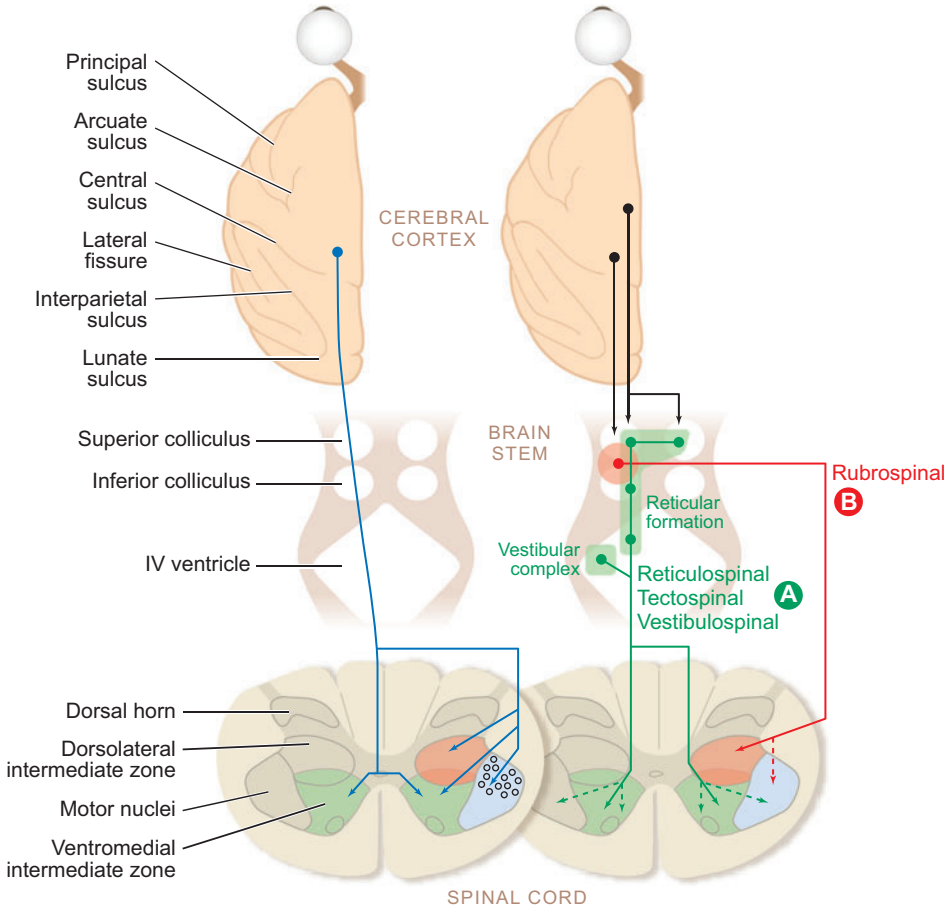


Figure 1

Schematic representations of the distributions of the corticospinal fibers and the fibers belonging to group A (ventromedial) and group B (dorsolateral) brainstem pathways, according to the scheme proposed by Kuypers (1981). On the right, Group A fibers (reticulospinal, tectospinal, vestibulospinal) are shown in green, arising from the brainstem reticular formation, superior colliculus, and vestibular complex. These fibers terminate bilaterally in the ventromedial part of the intermediate zone (IZ) shown as a green area in the spinal sections, with some direct projections to motoneurons supplying trunk and girdle muscles (dashed green lines). Group B fibers (rubrospinal) are shown in red, arising from the red nucleus. These fibers terminate contralaterally in the dorsolateral region of the IZ (shown in red in the spinal sections) with some projections to the lateral group of motor nuclei innervating the arm and hand (dashed red lines). These brainstem pathways receive significant cortical projections (black). On the left, corticospinal projections are shown in blue: Some parallel the group A fibers and terminate bilaterally in the ventromedial IZ (green area), whereas the majority parallel the group B system and terminate contralaterally in the dorsolateral IZ (red area) and directly on motoneurons innervating the arm and hand (blue region with small black circles).

dilation, cardiovascular changes, vocalization, micturition, and sexual behaviors. This lateral system influences the relevant motoneuronal groups through other brainstem pathways, such as the periaqueductal gray, which triggers limbic vocalization during mating, fear, etc. (Vanderhorst et al. 2000).

The corticospinal and corticobular pathways. These pathways are present in all

CS: corticospinal

EMG: electromyogram

CST: corticospinal tract

mammals but to very different extents. Kuypers (1981) saw the corticospinal (CS; blue fibers, left side of **Figure 1**) and corticobulbar (black fibers, right side of **Figure 1**) projections as acting in parallel with brainstem systems. In the more primitive forms (edentates, marsupials, and lagomorphs) any overlap in areas of CS termination with brainstem pathways is largely restricted to group B (i.e., rubrospinal) pathways.

In a second group of mammals, including rodents, carnivores, and primates, there is a much more extensive CS projection, reaching all levels of the spinal cord (cervical, thoracic, lumbar, and sacral) and innervating all regions of the spinal gray matter, including, motoneurons (shown as black circles, left side of **Figure 1**) in the ventral horn in primates. In these forms, CS terminations overlap with those of both A and B brainstem pathways. **Figure 1** (*left*) shows that corticospinal projections (*blue fibers*) terminate both bilaterally within the ventromedial IZ (*zone colored green in the spinal cord*) and contralaterally within the dorsolateral IZ (*red zone*); some of these crossed fibers also terminate in the motor nuclei (lamina IX; *blue zone* in **Figure 1**).

How useful is this categorization of pathways? Overall, the Kuypers scheme still makes an impact. For example, in the cat, stimulation within the medullary reticular formation evokes responses in proximal limb extensors and flexors bilaterally, responses that are strongly gated by the locomotor cycle (Drew, 1991), whereas reticulospinal neurons originating from the ponto-medullary reticular formation (PMRF) facilitate or suppress electromyogram (EMG) activity in proximal fore- and hind-limb muscles, again bilaterally. Similar observations have been made in the monkey (Davidson & Buford 2004, 2006; Davidson et al. 2007). These findings of bilateral influences on trunk and proximal limb muscles generally agree with those described by Kuypers for the ventromedial pathways (group A). The reticulospinal system is involved both in the control of locomotion and of the anticipatory postural changes needed to support these movements (Drew et al. 2004).

However, the divisions are certainly not absolute. Kuypers himself noted that some tectospinal and medullary reticulospinal fibers (group A pathways) also terminate in the lateral parts of the IZ (Alstermark et al. 1987, Holstege & Kuypers 1982) and therefore overlap with the terminations of both group B and CS projections, an overlap that is further enlarged by the extensive dendritic trees of both interneurons and motoneurons. New research in the macaque shows that stimulation within the PMRF and spike-triggered averaging from reticulospinal tract neurons show evidence of facilitation or suppression of EMG in more distal muscles, although these effects are far less common and weaker than for CS neurons (Baker & Riddle 2007).

Again, although the classical view of the corticospinal tract (CST) is that of a crossed pathway, a significant number of projections influence the ipsilateral spinal gray matter in the cervical (Galea & Darian-Smith 1997) (see **Figure 1**, *left*) and lumbosacral enlargement (Lacroix et al. 2004). These projections are of considerable potential significance for understanding the effect of cortical or spinal lesions.

The significance of collaterization. Descending pathways give off axon collaterals all along their route of descent toward and within the spinal cord. Kuypers noted that some pathways (e.g., group A) were more highly collateralized than others (e.g., the CST). He suggested that the latter exerted more focused actions and could mediate the more fractionated type of movements that characterize the use of the distal extremities, the hand and foot. The work of Shinoda and colleagues has since accumulated much evidence to show that highly collateralized vestibulospinal tract axon systems can actually subserve selective and coordinated head and neck movements in response to sensory input from the vestibular system (Sugiuchi et al. 2004).

DOES A DESCENDING PATHWAY CARRY OUT SINGLE OR MULTIPLE FUNCTIONS?

A single neuroanatomical pathway can mediate many different functions (Lemon & Griffiths 2005). The CST provides an excellent example; its functions include (*a*) descending control of afferent inputs, including these nociceptive inputs (Cheema et al. 1984, Wall & Lidierth 1997); (*b*) selection, gating, and gain control of spinal reflexes (Pierrot-Deseilligny & Burke 2005); (*c*) excitation and inhibition of motoneurons (Alstermark & Lundberg 1992, Porter & Lemon 1993, Maier et al. 1998); (*d*) autonomic control (Bacon & Smith 1993); (*e*) long-term plasticity of spinal cord circuits (Wolpaw 1997); and 6) trophic functions (Martin et al. 1999).

IS THE CORTICOSPINAL TRACT A MOTOR PATHWAY?

The anatomical characteristics of the CST support this multifunctional view. The CST originates from a wide variety of cortical areas, each with different functions, including, in the monkey, the primary motor cortex (M1), the dorsal and ventral premotor cortices, supplementary motor area (SMA), and cingulate motor areas (see Dum & Strick 2005). CS projections also extend from the parietal lobe (primary somatosensory cortex, S1), the posterior parietal cortex, and the parietal operculum. The origins of the CST from many different functional areas make it unlikely that the CST projection subserves a single role. In addition, the CST terminates widely within the spinal gray matter, presumably reflecting control of nociceptive, somatosensory, reflex, autonomic, and somatic motor functions. Although CS projections from different frontal cortical areas show a similar overall pattern (He et al. 1993), studies show marked quantitative differences in the projections, for example, from SMA vs. M1 (Maier et al. 2002; Boudrias et al. 2006).

The CST's involvement in controlling more than one function raises questions about its classical role as a motor pathway. Indeed, the CST projection to the dorsal horn is found in all mammals, and the early evolution of the CST to control afferent input may reflect the earliest evolved form of supraspinal control exerted by the CST (Kuypers, 1981, Jones 1986, Canedo 1997, Lemon & Griffiths 2005). In monkeys, the projection to the dorsal horn is derived from S1, not from M1 (Jones 1986, Armand et al. 1997). CST projections to the dorsal horn are probably involved in the descending control of proprioceptive inputs generated by movement or sensory reafference and the gating or filtering of such inputs to both local central pattern generators (CPGs) and supraspinal centers (Wolpert et al. 2001). CST projections to the dorsal horn are an important source of presynaptic inhibition of primary sensory afferent fibers (Canedo 1997, Wall & Lidierth 1997), and this mechanism could allow removal of predictable sources of afferent input associated with feedforward motor commands for voluntary movement. Lesions of the CST cause a breakdown in fine sensorimotor control, implying a deterioration not only in motor function, but also in the capacity to interrogate correctly the sensory feedback from the hand (Lemon & Griffiths 2005).

M1: primary motor cortex

SMA: supplementary motor area

CPG: central pattern generator

IS THE ORGANIZATION OF THE DESCENDING PATHWAYS HIGHLY CONSERVED ACROSS DIFFERENT MAMMALIAN SPECIES?

Many basic motor activities (e.g., breathing, swallowing, locomotion) are common to all mammalian species, and some studies suggest that the main function of the descending pathways is to modulate the CPGs that control each of these activities (Dietz 2003, Drew et al. 2004, Grillner & Wallen 2004, Yang & Gorassini 2006). Because the basic neuronal mechanisms underpinning these activities are present in all species, one can argue that the descending pathways should exhibit a highly conserved organization pattern across different species, and indeed, some CS and reticulospinal neurons are active during both locomotion and reaching

CM: cortico-motoneuronal[1]

(Drew et al. 2004), as originally suggested in an influential paper by Georgopoulos & Grillner (1989).

However, Grillner & Wallen (2004) also note that the control of some movements, such as independent fine movements of the fingers, are exceptions to this scheme. Indeed, an emerging view of the descending pathways is that although an overall pattern is recognizable, considerable variations exist across species in the organization of the descending pathways, and particularly of the CST. Two examples of such differences are considered here: first, wide variation in the extent of direct cortico-motoneuronal (CM) connections in different primates and absence of this system in non-primates, and second, species differences in the organization of motor effects transmitted from the CST to motoneurons via propriospinal neurons.

The CM System is Developed to Different Extents across Species

The CM system, first discovered by Bernhard & Bohm (1954), represents a direct, monosynaptic projection from some CS fibers to spinal motoneurons.

Non-primates. Kuypers first showed that striking differences exist in the degree of CM system development across different species (Kuypers 1981). A number of studies have now confirmed that the CM system is a uniquely primate feature; there are no functional CM connections in the cat (Illert et al. 1976), rat (Yang & Lemon 2003, Alstermark et al. 2004), raccoon (Gugino et al. 1990), or mouse (Alstermark & Ogawa 2004) (see **Figure 2**).

Non-human primates. The CM system is developed to a variable extent in different primates (Lemon & Griffiths 2005). It is absent in tree shrews, lemurs, and marmosets. It is well developed in some New World monkeys, such as the capuchin monkey, and in Old World monkeys, including the macaque (**Figure 2**); CM connections are generally most numerous in the great apes (Kuypers 1981). Bortoff & Strick (1993) made a direct comparison of the anterograde labeling in the cervical enlargement that resulted from injections into motor cortex of two New World species: the capuchin monkey (*Cebus appella*) and the squirrel monkey (*Saimiri sciureus*). Whereas the labeling of CST terminations in the IZ was similar in the two species, the labeling in the ventral horn was remarkably different. In *Cebus*, dense projections into lamina IX extended into the most lateral and dorsal motor nuclei that innervate the intrinsic hand muscles, whereas CST projections into the ventral horn in *Saimiri* were much more sparse.

When assessed electrophysiologically, the CM input to hand and forearm motoneurons in the squirrel monkey, *Saimiri*, is weak compared with that in the macaque (Nakajima et al. 2000), where there are strong functional CM connections to hand and digit muscles (**Figure 2**) as well as somewhat weaker connections to muscles acting more proximally (Porter & Lemon 1993, McKiernan et al. 1998). Evidence also demonstrates CM connections to foot and tail motoneurons (Jankowska et al. 1975; see Porter & Lemon 1993).

Humans. Anatomical evidence supports the existence of CM projections in human material (Kuypers, 1981) and monosynaptic effects on hand-muscle motoneurons in awake volunteers (**Figure 2**) (Palmer & Ashby 1992, Baldissera & Cavallari 1993, de Noordhout et al. 1999) as well as on many other upper limb muscles, even those acting at proximal joints (Colebatch et al. 1990). CM effects on lower limb muscles are also well defined (Brouwer & Ashby 1990, Rothwell et al. 1991, Nielsen et al. 1995).

Functional significance. Investigators are still debating the functional significance of these species differences for sensorimotor

[1]The term cortico-motoneuronal is quite specific to this particular monosynaptic connection and should not be used to refer to more general cortical influences over motoneurons mediated by oligosynaptic pathways.

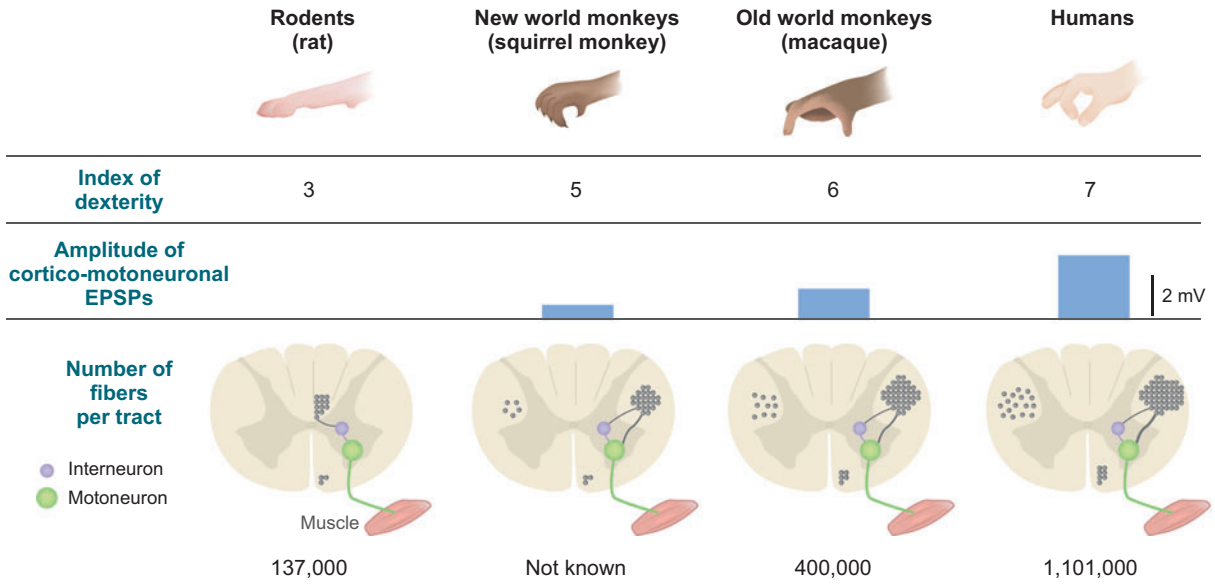


Figure 2

Relationship between the development of the CST and the emergence of fine motor control abilities. In rodents, there are no direct connections between CS neurons and the cervical motoneurons which innervate forelimb muscles—brainstem pathways and spinal interneurons relay cortical input to motor neurons. Most of the CST fibers in rodents travel in the dorsal columns. In non-human primates and humans, direct CS connections with motoneurons have evolved, together with an increase in the size and number of the CS fibers. This is reflected in an increase in the size of the excitatory postsynaptic potential (EPSP) elicited by cortical neurons in hand motoneurons. The primate CST is located mostly in the lateral columns, and a significant proportion of CS fibers (~10%) descend ipsilaterally. Development of the CST correlates with the improvement in the index of dexterity, particularly in the ability to perform finger-thumb precision grip (with permission from Courtine et al. 2007).

control of the hand (Lemon & Griffiths 2005, Iwaniuk et al. 1999) (see **Figure 2**). Heffner & Masterton (1983) already established the relationship across species between the extent of CST projections among the motoneuron pools of the spinal gray matter and the index of dexterity, a linear score of hand function that reflects the use of digits for prehensile purposes and for manipulation. For example, the capuchin monkey, *Cebus*, with many CM projections to hand motoneuron pools, is a very dexterous monkey and uses a pseudo-opposition between the tip of the thumb and the side of the index to grasp and manipulate small objects (Fragaszy 1998) and to use tools (Phillips 1998). In contrast, the squirrel monkey, *Saimiri*, with much weaker CM projections, has no precision grip and limited manipulatory skills.

The available data suggest that the CM system is a recently evolved feature and that it subserves evolutionarily new aspects of motor behavior, including voluntary control of relatively independent finger movements. Although such movements are not exclusive to species with CM connections, they are far better developed in primates than in non-primates.

Variation across Species in the Development of Propriospinal Transmission to Motoneurons

Descending excitation from the cerebral cortex is also transmitted from the CST to forelimb motoneurons (C6-Th1) through two rather different interneuronal routes: one via segmental interneurons (**Figure 2**) located in the same lower cervical segments (C6-T1) as the forelimb motoneurons, and the other via propriospinal neurons (PNs; i.e., interneurons located outside the forelimb segments),

PN: propriospinal neuron

PT: pyramidal tract

including those located in upper cervical segments (C3-C4). These are part of a propriospinal system that is present throughout the spinal cord (Molenaar & Kuypers 1978). After spinal injury, PN mechanisms may provide a means of reestablishing voluntary motor control without the need to regenerate long fiber tracts over the full length of the spinal cord (Fouad et al. 2001).

Cat. A large number of electrophysiological, anatomical, and lesion studies showed that the C3–C4 PNs are involved primarily in mediating the descending command for forelimb target reaching, whereas the local segmental system mediates the descending command for food taking (grasping a morsel of food with the digits) (Alstermark & Lundberg 1992; see Isa et al. 2007).

Non-human primates. Since the pioneering studies were carried out in the cat, considerable attention has been focused on whether this type of organization is seen in other species. The overall conclusion at present indicates that there are quite striking variations in the organization of propriospinal transmission of CS excitation to motoneurons (Isa et al. 2007). Once again, studies show differences between different primates: In the New World squirrel monkey (*Saimiri*), effects in upper limb motoneurons consistent with transmission through a C3-C4 PN system were observed, although these effects are significantly weaker than in the cat (Nakajima et al. 2000).

In the intact macaque monkey, such effects are rare (Maier et al. 1998, Alstermark et al. 1999, Olivier et al. 2001). Maier et al. (1998) speculated that this was because transmission through the C3-C4 system had been replaced by excitation mediated by the CM system. Alstermark et al. (1999) subsequently demonstrated that C3-C4 transmission can occur in the macaque monkey but only after the systemic administration of strychnine (Alstermark et al. 1999), which is a glycinergic antagonist and which therefore produces widespread abolition of inhibition in the spinal cord. Since then, studies have shown that in the intact macaque monkey, stimulation of the pyramidal tract (PT) evokes feedforward and feedback inhibition of C3-C4 PNs, which may prevent onward transmission of excitation to upper limb motoneurons when the whole PT is stimulated (Isa et al. 2006, 2007).

Thus several striking differences exist between cat and macaque monkey: First, studies show more CS inhibition of C3-C4 PNs in the monkey than in the cat. A strychnine study has not yet been published for the cat, so we do not know how big the differences are. Second, although 84% of C3-C4 PNs in the cat project an ascending axon collateral to the lateral reticular nucleus (hypothesized to be an ascending readout of PN activity; Alstermark & Lundberg 1992), this projection was found for only 30% of PNs in the macaque (Isa et al. 2006). Finally, even after strychnine, it requires three or four high-frequency shocks to the PT to discharge the sampled PNs, which is not consistent with a powerful excitatory linkage between the CST and these PNs.

Rodents. A recent study by Alstermark et al. (2004) found no evidence of C3-C4 transmission of CS excitation to forelimb motoneurons in the rat; instead, they found that the cortex influenced motoneurons through corticoreticulospinal pathways. In the mouse, few motor effects on forelimb motoneurons are evoked from the CST, and reticulospinal control seems to be more important in this species (Alstermark & Ogawa 2004).

Conclusion: species differences in organization of descending pathways for motor control. Differences in the organization of CS projections across species may well reflect differences in the functional contributions made by this system and may explain species-dependent effects of CST lesions. Therefore, one should exercise caution in selecting which animal model should be adopted when interpreting the very considerable amount of indirect evidence for C3-C4 transmission in humans (Pierrot-Deseilligny and Burke 2005),

and also in understanding changes that occur after spinal cord injury, stroke, and other disorders (Lemon & Griffiths 2005, Courtine et al. 2007).

WHAT IS THE FUNCTIONAL SIGNIFICANCE OF DIRECT CONNECTIONS WITH TARGET MOTONEURONS?

In addition to terminating in the IZ, several descending pathways produce monosynaptic actions on motoneurons, including fibers running in the rubro-, reticulo-, vestibulo-, and corticospinal tracts. These monosynaptic connections allow a direct contribution to motoneuron control, which operates in parallel with that from more indirect connections, possibly by adding the final spatiotemporal excitation patterns that would induce appropriate levels of motoneuronal recruitment and discharge (Lemon et al. 2004).

Some reviewers have taken the view that the CM input is unimportant because its excitatory input is rather small, rather like that of other monosynaptic inputs from other descending pathways (Baldissera et al. 1981, Grillner & Wallen 2004). An informed answer to this question requires the following issues to be addressed: (*a*) How extensive is the CM projection? (*b*) How many CM cells project to a given motoneuron or to a given muscle? And (*c*) how large are the postsynaptic CM effects in a given motoneuron?

New Details on the Origin of the CM Input from Viral Retrograde Tracer Studies

Fresh insights have come from recent work by Rathelot & Strick (2006) on the CM projection in the macaque monkey, using transneural labeling with rabies virus. Their approach has, for the first time, made it possible to identify anatomically the cells of origin of the CM projection to hand muscles in the macaque monkey. The rabies virus, when injected into the test muscle, is transported retrogradely and infects all the motoneurons of the injected muscle (first-order labeling; see **Figure 3**). The virus is subsequently transferred trans-synaptically to all the neurons that project directly to the infected motoneurons. This second-order labeling therefore involves different classes of neurons in the spinal cord (e.g., segmental interneurons, primary afferents), brainstem (e.g., cells of origin descending pathways), and cortex (CM cells). Subsequent third-order transneuronal transfer labels all the neurons, which project to these different classes of second-order neurons. In a typical experiment,

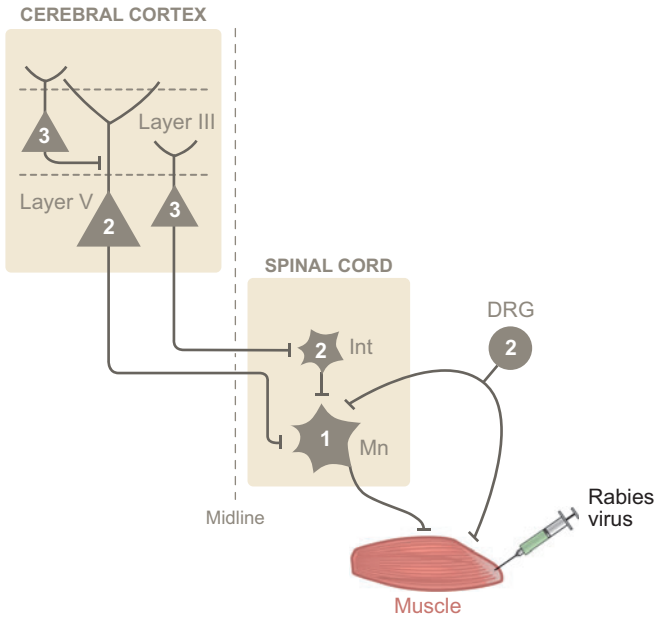
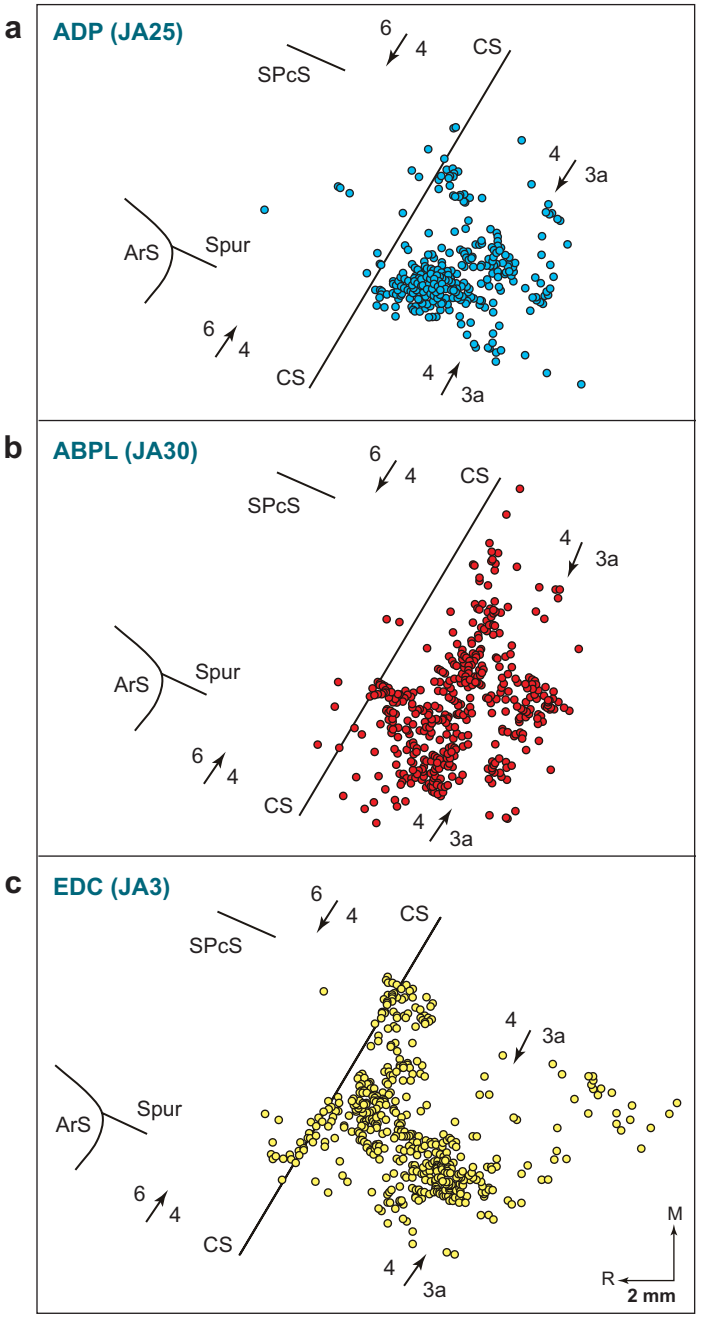
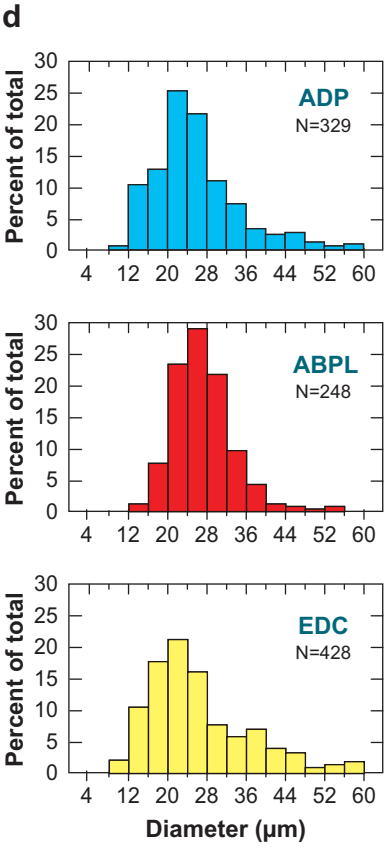


Figure 3

Retrograde viral tracing method for labeling CM cells in the macaque monkey. When the rabies virus is injected into a single digit muscle, it is transported in the retrograde direction to infect the motoneurons (i.e., first-order neurons, 1) that innervate the muscle. Then the virus is transported transneuronally in the retrograde direction to label all the second-order neurons (2) that synapse on the infected motoneurons. These include dorsal root ganglion cells that supply group Ia muscle spindle afferents, spinal cord interneurons, and cortical neurons in layer V (CM cells). At longer survival times, the virus can undergo another stage of retrograde transneuronal transport and label all the third-order neurons (3) that synapse on the infected second-order neurons. For example, the virus can move from second-order neurons in layer V to third-order neurons in layer III. Similarly, the virus can move from second-order interneurons in the spinal cord to third-order cortical neurons in layer V. DRG, dorsal root ganglion cell; Int, interneuron; Mn, motoneuron; 1, first-order neuron; 2, second-order neuron; 3, third-order neuron (from Rathelot & Strick 2006 with permission).

first-order labeling of motoneurons is seen three days after muscle injection, with second-order labeling 3.5–5 days after injection and third order labeling after still longer survival times. By carefully timing their experiments, Rathelot & Strick (2006) were able to ensure that the transneuronal labeling process had not gone beyond the second-order stage so that any labeled cortical neurons could be confidently identified as CM.





The labeled CM cells were distributed over a broad territory located in the classical arm and hand area of M1 (see **Figure 4*a–c***). Most of the labeled CM neurons were found in the caudal part of classical M1, in the rostral bank of the central sulcus, and very few were found on the convexity of the precentral gyrus. The CM projection was therefore not coextensive with the total CS projection from M1, in keeping with older degeneration studies of the CM projection (Kuypers & Brinkman 1970).

The area of M1 that contained the entire population of CM cells innervating an individual muscle was quite large and measured between 42 and 54 square mm. It overlapped heavily with representations of other hand muscles (see **Figure 4*a–c***). These findings finally rule out the existence of a fine, nonoverlapping, somatatotopic mapping of hand muscles within M1, thus concluding a long-running debate (Asanuma 1975, Andersen et al. 1975, Phillips 1975, Lemon 1988, Schieber & Hibbard 1993). The extensive representation of a single hand muscle reaches into regions of M1 concerned with elbow and shoulder movements (Kwan et al. 1978, Park et al. 2001) and suggests that this "could provide the neural substrate to create a broader range of functional synergies" involving hand and digit muscles as well as those acting at more proximal joints (see McKiernan et al. 1998).

The number of CM cells labeled from the three muscles, belonging to the cortical colony of that muscle (Andersen et al. 1975), varied between 248 (AbPL) and 428 (EDC); EDC is a larger muscle than AbPL. If a significant proportion of the CM cell colony converging on a hand muscle was active, and the unitary excitatory postsynaptic potential (EPSPs) from each CM cell motoneuron contact were within the range of other descending systems, this would produce a significant total excitatory drive (see below).

EPSP: excitatory postsynaptic potential

STA: spike-triggered average

CM Cell Activity during Voluntary Movement

I cannot review here the very extensive literature that shows that CM cells in monkey M1 cortex are highly modulated during skilled hand and digit movements and the studies that show patterns of activity that are congruent with their connectivity as established by spike-triggered average (STA) (Bennett & Lemon 1996, Jackson et al. 2003, Schieber & Rivlis 2007). Information on how this activity is transformed into appropriate patterns of motoneuron activity is only just coming to light (Yanai et al. 2007). CM cells may also be involved in the generation of transcortical reflexes (Cheney & Fetz 1984), which could underpin fast and powerful responses to peripheral perturbations (Johansson et al. 1994).

CM Projections from Secondary Cortical Motor Areas?

Rathelot & Strick (2006) have not yet reported any labeled CM neurons in the

Figure 4

(*a–c*) Cortical surface maps of CM cells that innervate the motoneurons for digit muscles. Each panel (*a–c*) displays a flattened or unfolded map of the central sulcus and precentral gyrus showing location of CM cells (*small round symbols*) labeled after injections of the rabies virus into ADP (adductor pollicis), ABPL (abductor pollicis longus) or EDC (extensor digitorum communis). Each muscle was injected in a different monkey (JA25, JA30, and JA3, respectively). Small arrows are placed at the area 4–6 border and the area 4–3a border. ArS, arcuate sulcus; CS, central sulcus; M, medial; R, rostral; SPcS, superior precentral sulcus. Note the large area occupied by the CM representation or colony belonging to each muscle and the extensive overlap between the three colonies. (*d*) Size distribution of the somata of CM cells. The graphs show the size of CM cells in M1 labeled after virus transport from ADP (*top*), ABPL (*middle*), and EDC (*bottom*). Cell size in these graphs represents the average of a cell's maximum and minimum diameter. Note the large proportion of small cells comprising the CM colony (from Rathelot & Strick 2006 with permission).

secondary motor areas: SMA, cingulate motor areas, or dorsal and ventral premotor areas, all of which give rise to CS projections (Dum & Strick 2005). In keeping with this, Maier et al. (2002) were unable to find evidence of CM-EPSPs in hand motoneurons evoked from intracortical stimulation in the SMA. In contrast, when the M1 hand area in the rostral bank of the central sulcus was stimulated, such EPSPs were evoked in most motoneurons tested. Stimulation of ventral premotor cortex (PMv) also failed to evoke CM-EPSPs in hand motoneurons (Shimazu et al. 2004). However, PMv stimulation could produce powerful modulation of M1 CS outputs (**Figure 5**), which may represent an important parallel route through which

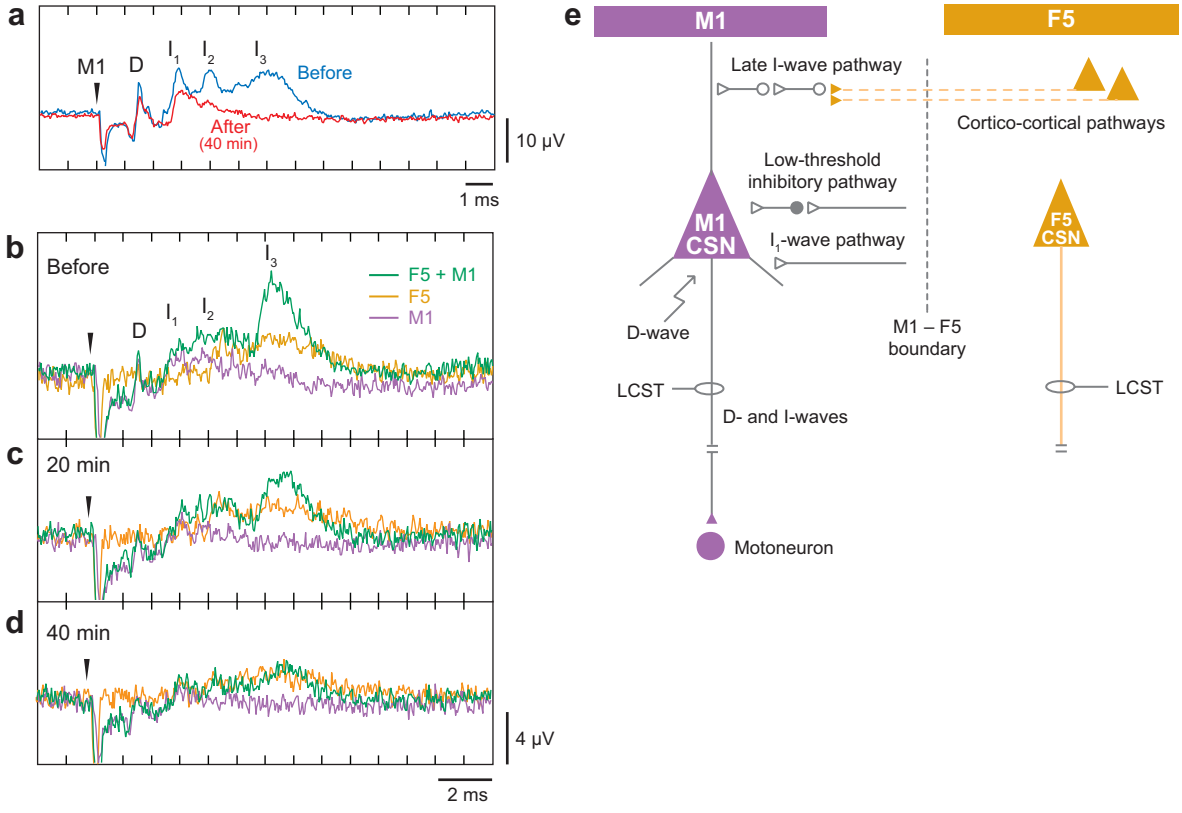


Figure 5

Facilitation of CS outputs from M1 from ventral premotor cortex (area F5). (*a*) Intracortical stimulation with a single pulse in the hand area of M1 evokes a series of descending CS volleys: the D (direct) wave and a number of indirect (I) waves (*blue trace*). Forty minutes after microinjection of the $GABA_a$ agonist, muscimol, close to the M1 stimulation site the late I waves (I_2, I_3) are mostly abolished (*red trace*); there is a small reduction in the I_1 wave and no obvious effect on the D wave. Averages of 150 sweeps, volleys recorded from the C3 spinal level. (*b–d*) Effects of muscimol injection in M1 on F5–M1 interaction. A single test (T) M1 shock was conditioned (C) by a single shock to the F5 division of PMv (*green*). Responses to the F5 shock alone are *orange* and to the M1 shock alone are *purple*. With the C–T interval of 0 ms, there was a marked facilitation of the I_3 wave. Twenty minutes after muscimol injection (C), this facilitation was considerably reduced, and it was abolished after 40 min (D), suggesting that F5-M1 interaction occurred within M1 itself. Averages of 100 sweeps. (*e*) Possible mechanisms explaining facilitation of late I waves. The elements (*in gray, on the left side of the diagram*) represent the three classes of excitatory inputs to CSNs: the D wave, the I_1 wave, and the later (I_2 and I_3) waves. A low-threshold inhibitory input pathway is also shown. These four inputs are all excited by stimulation within M1. The model proposes that the main excitatory input from F5 to M1 converges on the late interneuronal pathways in M1 giving rise to the I_2 and I_3 waves, thereby allowing F5 to influence I wave generation in M1 CS neurons. Note that although M1 CS neurons project directly to hand motoneurons, this is not the case for those located in F5 (from Shimazu et al. 2004, with permission).

a secondary motor area could exert its motor effects (Cerri et al. 2003, Shimazu et al. 2004). Reversible inactivation of M1 hand area can reduce or abolish motor responses evoked from PMv (Schmidlin et al. 2006).

Estimating the Size of the CM Input

Estimates of the amplitude of the CM input to a motoneuron or muscle have been derived from their responses to electrical stimulation of the CST or M1, or from spike-triggered averages derived from single CM cells. Both approaches suggest that CM effects can be substantial, particularly for motoneurons supplying muscles acting on the hand and digits. In the anaesthetized macaque monkey, stimulation of the pyramidal tract evokes monosynaptic EPSPs in most upper limb motoneurons, with a wide range in the size of these effects from a few hundred microvolts up to 5–7 mV; the largest effects occur in motoneurons supplying intrinsic hand muscles (Porter & Lemon 1993). The mean value for the compound EPSP (representing the summed excitatory input from all fast-conducting CM axons terminating on a motoneuron) was estimated at ~2 mV. This figure is probably an underestimate because disynaptic inhibition often truncates the CM EPSP before it reaches its maximum (Maier et al. 1998). In the awake monkey, PT stimulation with single shocks is capable of discharging active motor units at monosynaptic latency with high probability (Olivier et al. 2001). In awake human volunteers, using transcranial electrical stimulation, the size of the compound CM-EPSP in hand muscle motoneurons has been estimated as at least 4–5 mV (de Noordhout et al. 1999).

Investigators find some drawbacks in using electrical stimulation of the cortex and PT, not the least of which is the unnatural and synchronous activation of many fibers together, which may well exert mixed excitatory and inhibitory effects on target neurons. The STA represents a more natural approach to the problem and, in addition, allows estimates of the excitatory CM influence of single motor cortex cells. CM cells can be identified in the awake animal and exert facilitation of motoneuron pools that is consistent with CM action (Fetz & Cheney 1980, Lemon et al. 1986). Although researchers now generally accept that the STA method reveals a spectrum of postspike effects in EMG (Baker and Lemon 1998; Schieber and Rivlis 2005), the strength of CM synapses is again underlined by STA findings. Even single CM cells can produce detectable changes in the discharge of both single motor units and multiunit EMGs recorded from hand and forelimb muscles, and the total CM input to motoneurons could provide a significant proportion of the facilitatory drive needed to maintain its steady discharge (Cheney et al. 1991).

CM Effects from Small, Slowly Conducting PTNs

Rathelot & Strick (2006) reported that labeled CM neurons had soma diameters ranging from 12 to 60 μM, the majority being small in size (see **Figure 4*d***). Thus the CM output is not restricted to the large pyramidal cells in layer V (the classical Betz cells). STA studies have also demonstrated CM effects from small, slower-conducting CST neurons (Fetz & Cheney 1980; see Porter & Lemon 1993). Recording and stimulation approaches are both biased toward larger neurons with fast-conducting axons, so the contribution from the much more numerous smaller CM neurons has likely been seriously overlooked (Maier et al. 1998).

What Can We Learn from Lesion Studies?

Implicit in modern concepts of a distributed motor network is the acceptance that the behavioral and other changes that result from lesions to a descending pathway cannot be interpreted any longer as simply being due to the removal of the lesioned pathway. There are fast, activity-dependent, plastic changes that occur soon after a lesion is placed in a descending pathway (Steward et al. 2003, Bareyre et al. 2004, Deumens et al. 2005, Vavrek et al. 2006). The behavioral outcome is a consequence of compensatory changes of the motor network as a whole, including the response

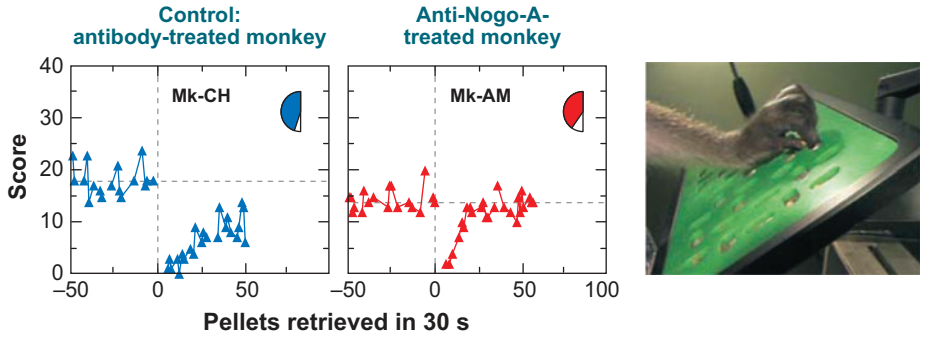


Figure 6

Effects of lesions to the CST at the cervical level on skilled independent finger movements in the macaque monkey, and partial recovery following treatment with anti-NOGO antibody. Data are shown for quantitative assessment of manual dexterity before and after lesion in a representative pair of monkeys (Mk-CH and Mk-AM), with similar extent of lesion in the dorsolateral funiculus at the C7-C8 border in the cervical spinal cord (the extent of the blue and red zones in the semicircular figures represents the extent of the hemicord lesion for each monkey). Monkeys were assessed on a modified Brinkman board (*right*) using the precision grip (opposition of thumb and index finger) to retrieve food pellets from the board. The untreated monkey (*blue*, Mk-CH) showed some limited recovery in its performance (score represents number of pellets retrieved in 30 s), but the monkey treated with the antibody to neutralize the neurite growth inhibitor Nogo-A (*red*, Mk-AM) rapidly returned to control levels of dexterity (from Freund et al. 2006, with permission).

of uninjured fibers, rather than a consequence of the removal of a single descending pathway or component. For example, lesions of the CST cause long-term changes in the influence of the rubrospinal tract (Belhaj-Saif & Cheney 2000). The exciting prospect is that this compensatory response can be boosted by appropriate therapies (see Case & Tessier-Lavigne 2005, Deumens et al. 2005, Buchli et al. 2007) (see **Figure 6**). Of course, spinal injury in humans results in damage to multiple ascending and descending pathways, and selective lesions of individual tracts are a poor model for such injury; however, they do provide important insights into the regrowth and possible regenerative capacities of different pathways.

Cortical and capsular lesions. These probably affect all the descending pathways because the cortex provides a major input to the cells of origin of the brainstem pathways (Kuypers 1981; see Matsuyama & Drew 1997, Matsuyama et al. 2004) (see **Figure 1**, *right*). Such lesions affect not only the CS and corticobulbar projections, but also corticostriatal, corticopontine, and other systems related to motor function. Indeed it is remarkable that clinically, capsular lesions give rise to the classical pyramidal signs of contralateral weakness, and especially those affecting the distal musculature (Colebatch & Gandevia 1989), despite the fact that CS fibers probably constitute only a few percent of the total number of ascending and descending fibers within the capsule. The importance of the integrity of the CS tract has recently been reemphasized by studies of recovery of precision finger movements after subcortical stroke (Lang & Schieber 2003, Ward et al. 2007); good recovery of function and a normal pattern of brain activation were found in those patients in whom transcranial magnetic stimulation demonstrated an intact CS projection from the damaged hemisphere. During human spinal surgery, continuous intraoperative monitoring, below the surgery level, of the CS D-wave evoked from the motor cortex can be very useful in preventing poor outcomes in terms of locomotor and other functions; loss of the D-wave is a strong indicator for paraplegia following surgery (Sala et al. 2006).

D-wave: Corticospinal activity reflecting direct activation of CS neurons

PYRAMIDAL AND CST LESIONS

Lawrence & Kuypers (1968a) originally showed that a complete pyramidotomy in the macaque monkey caused permanent deficits in skilled hand function, but we do not know how much of the deficit was due to interruption of CM projections (we must await a selective means of lesioning or inactivating the CM projection). Compared with the effects of complete pyramidotomy, a rather different picture emerges with subtotal lesions of the CST (Lawrence & Kuypers 1968a; see Porter & Lemon 1993). This applies to subtotal or unilateral lesions of the pyramidal tract and to funicular lesions or hemisections at the spinal level. Several recent studies have investigated the effect of unilateral surgical interruption of the fibers in the lateral CST at the cervical (Galea & Darian-Smith 1997, Sasaki et al. 2004, Freund et al. 2006) and thoracic levels (Courtine et al. 2005). The initial effects are similar to a complete CST lesion, with a striking deterioration in the speed, force, and accuracy of more distal hand (**Figure 6**) and/or foot movements, especially those involved in tasks demanding high levels of dexterity (e.g., catching with the hand or foot, removing food from small wells; **Figure 6**). The initial deficits must reflect the loss of CS connections to the spinal segments controlling the hand (or foot), including CM connections (Nishimura et al. 2007). The fast CM-EPSPs that are normally evoked in most hand motoneurons were absent after a C5 lesion by Sasaki et al. (2004). However, such lesions also sever the CS projections to segmental interneurons below the lesion (**Figure 2**), including those mediating inhibition of motoneurons.

Thereafter, these deficits often show a substantial degree of recovery, the extent of which seems to be related to the amount of CST fiber sparing; however, there is usually a permanent deficit of independent digit movements, and especially of the thumb. The subsequent recovery of grasping function (Sasaki et al. 2004, Freund et al. 2006) or of locomotor function (Courtine et al. 2005, Nishimura et al. 2007) after spinal CS lesions probably reflects the plastic changes induced elsewhere in the CNS, and we now know that there is significant sprouting of these fibers above the lesion (Fouad et al. 2001, Bareyre et al. 2004). Importantly, these changes can be further promoted by reducing the levels of inhibitory factors that suppress sprouting and regeneration, for example, by administration of antibody to the myelin inhibitory factor, NOGO (**Figure 6**) (Freund et al. 2007). The molecular identity of a given pathway must determine the capacity for sprouting, growth, and development of new synapses. It may also determine whether compensatory plasticity comes from uninjured fibers belonging to the same pathway or whether others can contribute, a key factor that might explain the substantial differences in the outcomes produced by total vs. subtotal lesions of a particular pathway.

Stimulation of the PT after a subtotal CST lesion evokes EPSPs in hand motoneurons with latencies longer than those for normal monosynaptic CM responses. These EPSPs could be disynaptic and originate from C3-C4 propriospinal projections (as suggested by Sasaki et al. 2004) but could also result from monosynaptic CM projections from slow uninjured CS fibres (as shown by Maier et al. 1998; see Lemon et al. 2004). This is potentially significant because of the large numbers of slow- vs. fast-conducting CS fibers and because fast fibers may be more susceptible to injury (Blight 1983, 1991; Quencer et al. 1992).

SUMMARY POINTS

1. Each descending pathway has specific characteristics that determine its neuronal targets within the spinal cord and therefore its functional role.
2. Each descending pathway may carry out a number of functional roles; these are linked together by the need for a coordinated set of operations underpinning performance of basic functions such as balance, posture, locomotion, and reaching.

3. Although some general principles underlie the organization of the descending pathways, striking differences can be found between species, and research suggests that, in the case of the corticospinal tract (CST), these differences reflect species-specific features of sensorimotor behavior, including differences in skilled use of the hand and digits.
4. The cortico-motoneuronal (CM) system provides the capacity for fractionation of movements and the control of small groups of muscles in a highly selective manner, an important feature of skilled voluntary movements in the acquisition of new motor skills. The CM system may provide an efferent pathway that is accessed by the extensive motor network of the primate brain for development of adaptive motor programs.
5. The CM system works in parallel with other indirect corticospinal (CS) influences, transmitted through segmental interneurons and propriospinal neurons; in some primates, the contribution of the CM inputs can be considerable.

FUTURE ISSUES

1. We need to understand the role of the CST in controlling or gating sensory afferent input. How exactly does it function to remove unwanted reafference?
2. We also need to understand how the movement-related information generated by the cells of origin of the descending pathways is integrated by spinal interneurons and motoneurons.
3. We need a better understanding of the compensatory mechanisms that are triggered by damage to different motor pathways.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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