Selection and Initiation of Motor Behavior

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Abstract

Successful locomotion in vertebrates requires not only generation of the appropriate propulsive synergy (flying, swimming, or walking), but also goal-directed steering and control of body orientation. In most vertebrates, a correct positioning of each foot is also required during selected phases of the movement. This review focuses on the role of the forebrain and brainstem control in the initiation of locomotion. It considers the basal ganglia, hypothalamus, the mesencephalic locomotor region, including the cuneiform and pedunculopontine regions, as well as the medullary reticular areas. The various corticospinal systems are also reviewed because they most likely contribute to accurate foot placement during locomotion over a complex terrain.

In the absence of their forebrain, mammals like decerebrate cats and rats can be made to walk, trot, and gallop by activation of different locomotor regions in the brainstem. Corresponding findings have been made in all classes of vertebrates. The movements are well coordinated and accompanied by a largely appropriate equilibrium control. In character, however, the movements are robotlike—neither goal directed nor adapted to the environment. The latter qualities are added by neural structures in the forebrain. However, even in advanced mammals like the cat, goal-directed locomotion is retained after an ablation of the entire cerebral cortex that leaves the rest of the forebrain intact (including the basal ganglia and hypothalamus). Kittens, decorticated during their first few weeks of life (Bjursten et al., 1976), can be kept alive for years. The casual observer finds it difficult to distinguish their movements from those of cats with intact nervous systems. They exhibit periods of rest (and possibly sleep), become active, search for food, and are able to remember the location of food. Complex patterns of behavior, such as searching for and finding water or food, or attacking other individuals, require a sequential recruitment of the motor programs coordinating locomotion in combination with other motor patterns. Such patterns of behavior can be so activated without the participation of the cerebral cortex. The neuronal substrate contained in a forebrain devoid of the cerebral cortex is thus able to produce surprisingly complex, goal-directed patterns of behavior.

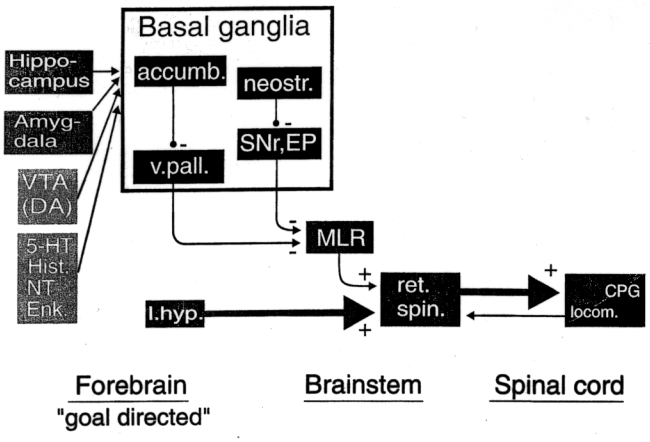

Figure 1.1
Forebrain and brainstem structures important for initiation of the basic locomotor synergy in mammals. The basal ganglia are included within the box (accumb, n. accumbens; v.pall., ventral pallidum; neostr., neostriatum; SNr,EP, substantia nigra pars reticulata, n. entopeduncularis). The inputs to accumb are indicated to the left, including modulation by dopamine (DA) from the ventral tegmental area (VTA) and also by 5-HT, histamine (Hist.), neurotensin (NT), and enkephalin (Enk.). The descending control from the MLR activates reticulospinal neurons (ret. spin.), which in turn activate the spinal central pattern generator (CPG). The reticulospinal neurons can also be activated by a direct projection from the lateral hypothalamus (l. hyp.).

Stimulation of different areas in the basal forebrain, such as the lateral hypothalamus, can evoke different types of goal-directed behavior (Hess, 1949) related to fluid and food intake, attack/escape behavior, or sexual behavior and drive. An important component of these different patterns of behavior is the locomotion that brings the animal to or away from a particular location. Locomotion itself is dependent on several different control systems (see Grillner, 1981, 1985; Mori, 1987; Shik and Orlovsky, 1976), including those that: (1) produce the actual propulsive moments (walking, flying, or swimming); (2) maintain body orientation (balance) during locomotion; (3) ensure that each foot is placed appropriately during each step (visuomotor coordination); and (4) plan the overall locomotor episode to bring the animal from one point to another through what often can be a complex terrain.

One brainstem locomotor area from which locomotion can be activated is termed the mesencephalic locomotor region (MLR), which appears to be present in all classes of vertebrates and is located at the mesopontine border lateral to the aqueduct. When stimulated, it produces the motor synergies underlying flying in birds (Steeves et al., 1987); walking in tetrapods (Shik et al., 1966; Eidelberg et al., 1981; also see review in Jordan, 1991); and swimming in fish and cyclostomes (McClellan and Grillner, 1984; Kashin and Feldman, 1974). Moreover, a simple continuous stimulation of this region can elicit locomotion involving the coordinated activation of hundreds of different muscles throughout the body. The more intense the stimulation, the faster the animal will locomote. The MLR projects to reticulospinal neurons in the lower brainstem, which in turn form the major locomotor pathway to the spinal cord. There is, in addition, a direct projection from the lateral hypothalamus to the reticulospinal locomotor activating system (Sinnamon and Stopford, 1987). This area appears to correspond to the area designated by Orlovsky (1970) as the subthalamic locomotor area. The axonal bundles from this area course through the ventral mesencephalon and appear to be distinctly different from the MLR system (figure 1.1). Thus, these two areas appear to have the independent capacity to elicit and control locomotor activity. They are referred to in this chapter as the MLR and the diencephalic locomotor region, respectively. An important consideration is obviously how the neurons in these areas are controlled and modulated by other regions of the central nervous system (CNS).

The Basal Ganglia and Locomotor Control in Mammals

If the caudate nucleus of the basal ganglia is removed selectively on both sides (in cat; Villablanca et al., 1976), a remarkable syndrome develops referred to as the "compulsory approaching syndrome." The cat will faithfully follow any moving object that catches its attention, seemingly unable to terminate the behavior (cf., also "obstinate progression"; Bailey and Davis, 1942). Although the exact limits of the lesions may be unclear, these results imply that the basal ganglia are involved in locomotor control. Mogenson and collaborators have shown that the older parts of the basal ganglia, n. accumbens and the ventral pallidum, take part in locomotor control (see figure 1.1). Administration of dopamine agonists or excitatory amino acids in n. accumbens elicits increased levels of locomotor activity (in rats, for example). These effects are obviated by local blockage of the MLR with lidocaine (see Mogenson, 1991; Slawinska and Kasicki, 1995), thereby suggesting that accumbens exerts its action via the MLR. Similarly, locomotor effects can also be elicited by activation of the excitatory input to n. accumbens from the hippocampus or amygdala, or by the dopaminergic input from the ventral tegmental area. Clearly, this part of the basal ganglia is involved in the control of locomotion.

The output from accumbens is made up of GABAergic, medium spiny neurons that project to the ventral pallidum. Neurons in the latter area project, in turn, to several areas including the MLR, as shown by both anatomical and electrophysiological criteria (Swanson and Mogenson, 1981). Part of these ventral pallidal projections are inhibitory (GABAergic), whereas other neurons or axons in this area appear to be excitatory, as shown in stimulation experiments (Mogenson, 1991).

The MLR appears to be under tonic inhibitory control under resting conditions because a local injection of bicuculline (a $GABA_A$ receptor antagonist) into this structure will cause a release of locomotor activity (Garcia-Rill et al., 1990). The dorsal pallidal output to the thalamus and superior colliculus provides a powerful tonic inhibition (a resting rate of output cell discharge near 90 Hz) and a release of different motor programs (such as specific saccades) through disinhibition (Hikosaka, 1991). As an analogy, the accumbens–ventral pallidum–MLR projection might release locomotion by a disinhibition of the MLR (see figure 1.1). If so, striatal GABAergic neurons, which are silent at rest, would become activated and thereby inhibit GABAergic ventral pallidal neurons, resulting in a disinhibition of MLR neurons. Although this scenario appears to be a likely possibility, it needs further investigation. For example, there is need to demonstrate that ventral pallidal neurons that project to the MLR have a high resting rate of discharge (in analogy to dorsal pallidal neurons) and that they become inhibited during initiation of locomotion. Injection of different GABA antagonists and uptake blockers into these relatively undefined areas have, however, produced conflicting results. There *may* be a neuronal link with double inhibition between n. accumbens and the MLR. This suggestion is compelling, but in need of further investigation.

The above-mentioned forebrain areas involve components of the dopaminergic "reward system" (ventral tegmental area), and they are implicated in diverse patterns of behavior (some involving the hippocampus and amygdala). Possibly these circuits are used to initiate locomotion in the context of different types of behavior, such as foraging and allied tasks (Kasicki et al., 1991; Sinnamon, 1993). The more recently evolved parts of the basal ganglia, such as the neostriatum–dorsal pallidum (globus pallidus–substantia nigra reticulata), may also play a role in locomotor control and perhaps in other behavioral contexts. The dorsal pallidum also projects to the MLR (Garcia-Rill and Skinner, 1986; Garcia-Rill, 1986). It seems likely that there are subcompartments in both neostriatum–dorsal pallidum and accumbens–ventral pallidum that are involved in the locomotor control.

The Lamprey Locomotor Control System

The lamprey system is much like the mammalian system (Grillner et al., 1995); it is a reticulospinal system that activates spinal pattern generators. The reticulospinal system can be activated from two areas corresponding to the MLR (McClellan and Grillner, 1984; Sirota et al., 1995) and the diencephalic locomotor region (El Manira et al., 1995). The input to the lamprey MLR is not yet known. The diencephalic locomotor region consists of cells projecting from the ventral thalamus area to neurons in the middle and posterior reticular nuclei of the rhombencephalon (MRRN, PRRN). They provide monosynaptic glutamatergic excitation to reticular neurons. When the diencephalic locomotor region is stimulated, fictive locomotor activity can be recorded in the spinal cord (El Manira et al., 1995, Pombal et al., 1995).

Cells in the diencephalic locomotor region receive a GABAergic projection from the ventral pallidum, which in turn receives input from GABAergic striatal neurons as deduced from immunohistochemical and tracing data (Pombal et al., 1995). Thus, evidence suggests that the lamprey CNS and the mammalian CNS utilize a similar locomotor circuit: a double inhibitory circuit. The input to the striatum is from the dorsal thalamus and selected telencephalic structures. In addition, there are a number of modulatory inputs, including dopamine, serotonin, histamine, neurotensin, and enkephalins (Pombal et al., 1995). Such organization of input is identical to that of mammals (see Graybiel, 1995), thereby providing evidence for an ancient organization of the vertebrate basal ganglia (the lamprey line of evolution became separate from the line leading up to mammals 450 million years ago).

Midbrain Locomotor Regions

Although the MLR is now well established as a functional region of the brain stem involved in the initiation of locomotion, the nature of the MLR activity in behaving animals is still an open issue. Two nuclei in the midbrain that have been implicated as the major components of the MLR are the *nucleus cuneiformis* and the *pedunculopontine nucleus*. The MLR area also includes other cell groups, but most recent studies have focused on one or the other of these two nuclei.

Shik and others (1967) first showed that stimulation of the mesencephalon could produce locomotion in decerebrate cats. Nucleus cuneiformis was regarded as the effective site. Work with intact cats revealed that electrical stimulation of an area corresponding to the nucleus cuneiformis produced a significant increase in the speed of locomotion (Sterman and Fairchild, 1966; Mori et al., 1989). Stimulus sites were located "within and around the nucleus cuneiformis, possibly including a part of the pedunculopontine nucleus" (Mori et al., 1989, p. 71). A great many studies have been conducted involving histological verification of sites with electrical stimulation and injection of neuroactive substances effective in eliciting locomotion in cats, rats, and guinea pigs. Such sites were invariably located in and around the nucleus cuneiformis (Amemiya and Yamaguchi, 1984; Brudzynski et al., 1986; Milner and Mogenson, 1988; Coles et al., 1989; Depoortere et al., 1990a, 1990b; Garcia-Rill et al., 1985; Garcia-Rill et al., 1983a, 1983b; Marlinsky and Voitenko, 1991; Mitchell et al., 1988a, 1988b; Mori et al., 1983; Mori et al., 1989; Shefchyk et al., 1984; Shefchyk and Jordan, 1985; Shimamura et al., 1984; Shimamura et al., 1987; Shimamura et al., 1990; Sirota and Shik, 1973; Steeves and Jordan, 1984). The MLR has also been localized in a few submammalian species, including the carp (Kashin and Feldman, 1974), lamprey (McClellan and Grillner, 1984), and stingray (Bernau et al., 1991). According to Bernau and coworkers, "the stingray MLR is associated with the caudal portion of the cuneiform nucleus."

The pedunculopontine nucleus was first implicated in the initiation of locomotion on the basis of its connections with limbic structures and the basal ganglia (Armstrong, 1986; Garcia-Rill, 1991; Skinner and Garcia-Rill, 1990; Skinner and Garcia-Rill, 1993; Mogenson et al., 1993; Reese et al., 1995a, 1995b; Inglis and Winn, 1995). Among researchers there is considerable confusion concerning the role of the pedunculopontine nucleus in the initiation of locomotion. It consists of both cholinergic and noncholinergic cells, with borders now considered to be defined by the presence of cholinergic neurons (Inglis and Winn, 1995; Reese et al., 1995a, 1995b). (Previous studies considered its borders to be somewhat broader; see Swanson et al., 1984.) Mogenson and coworkers (Brudzynski and Mogenson, 1985; Milner and Mogenson, 1988; Brudzynski et al., 1993) have ascribed the effects of stimulation, drug injection, and lesions to actions on the pedunculopontine nucleus, but their results may have involved other structures, including the nucleus cuneiformis. The pedunculopontine nucleus and nucleus cuneiformis are in such close proximity that any effects produced by electrical stimulation or drug injections cannot always be attributed clearly to one or the other. Garcia-Rill and Skinner (1987a, 1987b; Garcia-Rill et al., 1990) have used markers for cholinergic neurons to show convincingly that locomotion can be induced by electrical or chemical stimulation within the pedunculopontine nucleus.

Lesions within the MLR region must be rather large to eliminate locomotion evoked by stimulation of more rostral structures. Such large lesions are effective if they involve the nucleus cuneiformis as well as more ventral areas of the midbrain, including the pedunculopontine nucleus (Jordan, 1986). A recent case report shows that similar lesions in humans can prevent standing and stepping movements (Masdeu et al., 1994). In this instance, a hemorrhage at the pontomesencephalic junction—including the nucleus cuneiformis, pedunculopontine nucleus, and other nearby areas—was detected using magnetic resonance imaging. When limited to the pedunculopontine nucleus or the nucleus cuneiformis, smaller lesions in experimental animals may not result in a locomotor deficit (Shik et al., 1968; Sinnamon and Stopford, 1987). On the other hand, it is possible to reduce locomotor activity by procaine injections into the MLR (Brudzynski and Mogenson, 1985) or by excitotoxic lesions and cobalt injections into the MLR (Brudzynski et al., 1993). There is controversy, however, regarding whether the neurons affected by such lesions are located in the pedunculopontine nucleus or the nucleus cuneiformis (Inglis and Winn, 1995). Lesions of the pedunculopontine nucleus do not appear to produce deficits in spontaneous or drug-induced locomotion (Steckler et al., 1994; Inglis and Winn, 1995). Procaine injection into the pedunculopontine nucleus, however, appears to block locomotion elicited by stimulation of the lateral hypothalamus (Levy and Sinnamon, 1990).

Only brief episodes of chemically induced locomotion were produced with injection sites in the pedunculopontine nucleus in rats and cats (Garcia-Rill et al., 1990), but sustained locomotion occurred with sites in the nucleus cuneiformis (Garcia-Rill et al., 1985). Effective sites for chemically evoked locomotion in freely moving rats appear to be located predominantly in the nucleus cuneiformis and not in the pedunculopontine nucleus, as currently defined (Milner and Mogenson, 1988). The activity-dependent expression of *c-fos* following treadmill locomotion in rats is detectable in nucleus cuneiformis and not in the pedunculopontine nucleus area as defined by NADPH-diaphorase staining (Shojania et al., 1992; Livingston et al., submitted). Similarly, labeling with 2-deoxyglucose (Shimamura et al., 1987; Jordan, 1986) re-

vealed increased activity only in the nucleus cuneiformis as a result of MLR-evoked locomotion. Stimulation of the periaqueductal gray (Sandner and Di Scala, 1992) or of the medial hypothalamus (Leite-Silveira et al., 1995)—which produce flight or escape responses and defensive or aversive behavior with concomitant locomotor activity in freely moving animals—results in c-*fos* labeling in the nucleus cuneiformis. The pedunculopontine nucleus is labeled with c-*fos*, however, during REM sleep (Shiromani et al., 1992, 1995).

The suggestion that stimulation of the nucleus cuneiformis is associated with aversive or escape reactions has considerable support. In freely moving cats or rats such stimulation produces—in addition to locomotor activity—behavior suggesting that the animal is attempting to avoid a noxious stimulus and escape (Sirota and Shik, 1973; Mori et al., 1989; Depoortere et al., 1990a, 1990b). Injections of glutamate into the nucleus cuneiformis of freely moving rats results in freezing, darting, and fast running (Mitchell et al., 1988a, 1988b).

There is evidence that the pedunculopontine nucleus is associated with startle responses (Ebert and Ostwald, 1991). When GABA antagonists were injected into this structure, a "slight jump preceded each bout of locomotion" (Garcia-Rill et al., 1990). These authors also described "audiogenic stepping," induced when GABA antagonists were injected into a locomotor site in the inferior colliculus. Stimulation of the cochlear nuclei can elicit locomotion (Beresovskii and Bayev, 1988), and auditory-evoked potentials have been detected in the pedunculopontine nucleus (Reese et al., 1995a, 1995b), which appears to express c-*fos* in response to startle-eliciting acoustic stimuli (Reese et al., 1992). The cholinergic cells in the pedunculopontine nucleus appear to project to the pontine reticular nucleus, an obligatory relay station in the primary startle pathway (Koch et al., 1993). Perhaps the pedunculopontine nucleus is important for locomotor activity resulting from startle-eliciting stimuli.

Three types of locomotor systems that function in different behavioral or motivational contexts have been proposed (Sinnamon, 1993): an *appetitive* system, a *primary defensive* system, and an *exploratory* system—all eventually converging on lower brainstem locomotor areas. According to this view, the preoptic and perifornical/lateral hypothalamic locomotor regions and their connections make up the appetitive system, with a direct projection to the brain stem. The primary defensive system consists of the medial hypothalamic and perifornical regions, plus their connections with the central gray and the MLR. The exploratory system is said to involve the subpallidal area, including hippocampal projections to n. accumbens, as well as accumbens projections to the subpallidum, the zona incerta, and the pedunculopontine nucleus. If such separate channels exist at the diencephalic and mesencephalic levels, with the primary defensive system somewhat distinct from the overlapping appetitive and exploratory systems, then the pedunculopontine nucleus and the nucleus cuneiformis may be involved in locomotor activity related to different behavioral goals. Thus, the nucleus cuneiformis might be more related to the medial hypothalamus and associated structures, with a role in escape, flight, aversion, and defensive behavior. The pedunculopontine nucleus might be more related to subpallidal systems or exploratory locomotion. The MLR may, therefore, include subcomponents involved in locomotion produced in different behavioral contexts. If this is correct, then the results of lesions studies involving the MLR should be interpreted on the basis of their behavioral contexts.

Pontomedullary Locomotor Areas

In all species examined, the pathways for initiation of locomotion that descend to the spinal cord are considered to arise from reticulospinal cells. This view was originally expressed by Orlovsky (1970) and has been extensively reviewed (Grillner, 1981; Armstrong, 1986; McClellan, 1986; Arshavsky et al., 1988; Jordan, 1991; Skinner and Garcia-Rill, 1993; Rossignol, 1996). Considerable evidence indicates the involvement of a lateral *pontomedullary locomotor strip* and a more medial *medullary reticular formation* (Garcia-Rill and Skinner, 1987a, 1987b) in the initiation of locomotion.

The medial reticular formation (Skinner and Garcia-Rill, 1993) is the source of the reticulospinal cells that supply a "locomotor command" to spinal locomotor systems (figure 1.1). Locomotor defects result from lesions in the reticulospinal areas that receive input from the MLR (Zemlan et al., 1983). Reversible cooling (Shefchyk et al., 1984), GABA injections (Garcia-Rill and Skinner, 1987a, 1987b), and procaine injections (Marlinsky and Voitenko, 1991) into the medial reticular formation block locomotion induced by MLR stimulation and pontomedullary, locomotor-strip stimulation (Noga et al., 1991). Activation of neurons in the medial reticular formation with cholinergic agonists, substance P, and excitatory amino acids (Garcia-Rill and Skinner, 1987a, 1987b; Sholomenko et al., 1991; Noga et al., 1988; Kinjo et al., 1990) produces locomotion in mammals and birds.

Precise anatomical identification of the reticulospinal cells that form the descending locomotor command pathway has not yet been accomplished for any species. It is presumed that glutamatergic cells predominate in this pathway because initiation of locomotion from the brain stem can be blocked by antagonists of excitatory amino acids (Fenaux et al., 1991; Douglas et al., 1993; Hagevik and McClellan, 1994). The pharmacology of the descending control of locomotion has been reviewed recently (Jordan et al., 1992; Rossignol and Dubuc, 1994). For example, excitatory amino acids can elicit a locomotor rhythm when applied directly to the isolated spinal cord. In the lamprey, reticulospinal monosynaptic excitation of all types of neurons recognized as having a role in the central pattern generator (CPG) for swimming is mediated by excitatory amino acids (Ohta and Grillner, 1989). The same reticulospinal nerves provide monosynaptic excitatory postsynaptic potentials (EPSPs) to the inhibitory and excitatory interneurons responsible for the CPG operation.

Other descending pathways are also likely to be sufficient, however, including pathways that contain 5-hydroxytryptamine (5-HT or serotonin) and norepinephrine. The raphe-spinal system deserves special attention because 5-HT promotes the development of plateau potentials in spinal cord neurons (Kiehn, 1991). This system is effective for induction of locomotor activity in the isolated neonatal rat spinal cord (Cazalets et al., 1992; Cowley and Schmidt, 1994) and it is necessary for the initiation of oscillatory membrane behavior in *Rana temporaria* embryos (Sillar and Simmers, 1994). Application of 5-HT antagonists blocks pharmacologically induced locomotor rhythms in the isolated neonatal rat spinal cord (MacLean and Schmidt, 1995). 5-HT cells in the caudal raphe nuclei increase their firing rate during treadmill locomotion in freely moving cats (Jacobs and Fornal, 1993; Veasey and Fornal, 1995), and 5-HT levels increase in the spinal cord during locomotion (Gerin et al., 1995).

Cortical Contribution to Locomotor Movements

Thus far we have focused on forebrain and brainstem control of the basic propulsive locomotor synergy, but what specific adaptations are necessary for accurate foot placement during each step (see Armstrong, 1986)? This action requires elaborate visuomotor processing, and it appears to depend on intact corticospinal projections. Liddell and Phillips (1944) showed that a transection of the pyramidal tract in cats resulted in an inability to

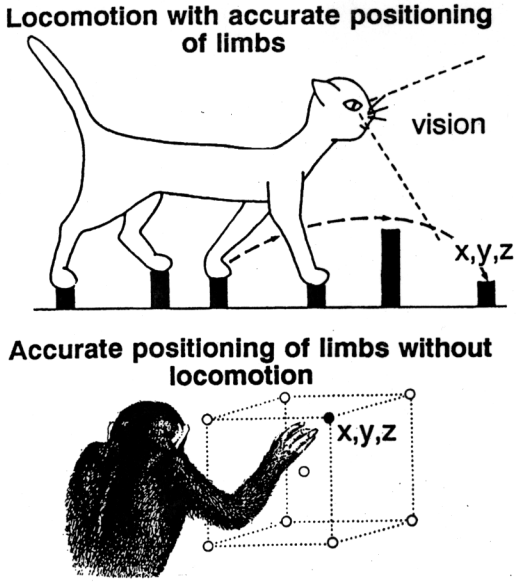

Figure 1.2
Precision movements during locomotion and reaching. During ordinary locomotion in a complex terrain, the limbs need to be placed with great accuracy (see drawing of a cat), which requires integration between general locomotor commands as well as corticospinal visuomotor coordination, leading to an accurate placement of the foot in each step. This aspect of visuomotor coordination has been shown to depend on a corticospinal contribution in the cat (see text), and presumably applies to other mammals. Arboreal primates move from branch to branch, and very accurate reaching and grasping are required in practically each step cycle. Positioning the limb accurately in relation to the environment, as the body is continuously moving, is in fact a more difficult task than a normal reaching situation. In this case, the body is kept semi-stationary while the arm and hand reach out to different points in the surrounding space. It is therefore likely that the neuronal systems used for accurate positioning of the limb during locomotion involve overlapping circuits to those used during reaching, as exemplified in the drawing of a monkey in the lower part of the illustration (A. P. Georgopoulos, S. Grillner, and G. N. Orlovsky, unpublished).

locomote on a ladder (which requires precise foot placement), but it had no effect on overground locomotion on a flat floor. The pyramidal tract includes projections from different precentral motor areas that are important in the control of a variety of motor patterns including reaching, grasping, and fine motor skills (Georgopoulos, 1991, 1995). Some types of locomotion (figure 1.2) over complicated terrain require adaptations for each foot placement, which, in their complexity, resemble reaching and grasping (Georgopoulos and Grillner, 1989). This analogy is the basis for the following review of cortical motor systems.

Precentral Motor Areas

The precentral motor areas comprise the motor cortex and several premotor areas anterior to it. These include,

from lateral to medial, the inferior premotor area, the arcuate premotor area, the dorsal premotor area, the supplementary and presupplementary motor areas, and the cingulate premotor area. The precentral motor areas have been investigated intensely for the past fifteen years, using both morphological and physiological methods. Here, we focus on new developments, especially those concerning the connectivity patterns and functional cell properties of these areas.

All premotor areas are interconnected with the motor cortex. In addition, precentral motor areas are interconnected with parietal areas of the ipsilateral hemisphere and with areas of the contralateral hemisphere. Recent studies (Johnson et al., 1996) have shown an orderly arrangement in the connectivity patterns such that frontal areas, from anterior to posterior (e.g., the dorsal premotor cortex to the motor cortex), connect with parietal areas, from posterior to anterior (e.g., medial intraparietal area, area 5), respectively. This pattern of anatomical connectivity is reflected in the discharge characteristics of cells in these areas (Kalaska et al., 1983; Johnson et al., 1996), suggesting that these interconnected areas process similar information with respect to arm movements (leg movements have not yet been studied).

C3/C4 System

Precentral motor areas can influence spinal interneuronal systems by influencing neuronal activity in the C3/C4 propriospinal system (Lundberg, 1979). This system is made up of interneurons that are intercalated between descending supraspinal systems and spinal segments innervating proximal muscles. Lesion studies in the cat (Alstermark et al., 1981) have provided evidence of a role for this system in reaching, and a general scheme has been proposed for the use of the C3/C4 system by descending precentral motor commands (Georgopoulos, 1988).

Thalamic Connections

Single thalamocortical axons in the cat terminate in the motor cortex in a multifocal pattern (Shinoda et al., 1992). Terminal plexuses are about 0.5 mm in diameter, separated by terminal-free gaps and distributed mainly in the rostrocaudal direction for a distance of up to 6 mm. A similar pattern has been observed for projections from postcentral to precentral areas in the monkey (DeFelipe et al., 1986). Conversely, there is substantial convergence of these projections as well, such that several nuclei converge on a small cortical area (Darian-Smith et al., 1990). The information conveyed to a small area in the motor cortex, therefore, comes from diverse sources, underscoring the highly integrative nature of motor cortical processing.

Another issue concerns the differential projections of the basal ganglia and cerebellum to various precentral motor areas. Motor and premotor areas receive partially overlapping input from the thalamus, and the bulk of the projections from thalamic nuclei receiving projections from the globus pallidus are directed to premotor areas (Shindo et al., 1995). Cerebellar influences to the motor cortex are also well established (Shinoda et al., 1992).

Corticospinal Projections

Pyramidal tract axons diverge and terminate along several spinal segments (Shinoda et al., 1981). Conversely, there is substantial convergence onto single motoneurons from a wide area of the motor cortex (Porter and Lemon, 1993). Thus, divergence and convergence are hallmarks of corticospinal projections. All precentral motor areas project to the spinal cord; some projections from premotor areas are as dense as those from the motor cortex (Dum and Strick, 1991). These findings have invalidated the earlier belief that premotor areas exert their influence on the spinal cord only by way of the motor cortex. It now seems that the precentral motor areas form a parallel system within which each premotor area, like the motor cortex, possesses a direct communication line with spinal structures.

Cortico-Brainstem Connections

There are extensive connections between all precentral motor areas and various brainstem structures, including the red nucleus, the reticular formation, and the pontine nuclei (Kuypers, 1981). The functional role of these connections is only partially understood but easy to infer when the recipient nuclei is considered to be a "relay" station (e.g., precerebellar nuclei). In most cases, this role still needs to be elucidated, as it does, for example, in the case of corticorubral and corticoreticular projection (Armstrong, 1986).

Microstimulation

Electrical microstimulation has been used to investigate the somatotopic organization of the motor cortex and to determine which motor variables are represented (Porter and Lemon, 1993). Microstimulation of a number of precentral motor areas can elicit motor responses. The result is in accord with the existence of direct projections from

these areas to the spinal cord. Microstimulation in the motor cortex results in activation of a number of muscles, and particular muscles can be activated from various locations. Interestingly, the motor cortex has "silent" zones in which microstimulation does not elicit motor responses (Waters et al., 1990). These zones are found between the hand and face representations. Neuroanatomical studies (Huntley and Jones, 1991) have documented a separation between the two representations and have also demonstrated extensive local connectivity *within* the forelimb and face representations but a lack of connectivity *between* these two representations.

Postspike Facilitation

The technique of spike-triggered averaging has been applied to motor cortical discharge in an attempt to determine the patterns of possible facilitation of motor cortical spike trains on electromyographic (EMG) activity (Porter and Lemon, 1993). The main finding was that postspike facilitation can be produced in a number of muscles of the contralateral forearm, hand, and fingers. Recently, postspike facilitation was observed in extensive groups of muscles spanning two or more joints (McKieman et al., 1994). This suggests that monosynaptic connections extend to large groups of muscles spanning several joints and that this pattern may be the substrate for integrated muscle synergies during reaching.

Combined Behavioral-Neurophysiological Studies

Recordings of single-cell activity in behaving monkeys, and to a lesser extent in cats, have provided important insights into the differential role of various precentral areas in motor control. It is important to realize that the behavioral task used in a particular experiment is crucial for interpreting the results. All tasks involve the generation of arm or hand movements under various conditions, which may relate to (1) the kind of motor output itself (e.g., making a movement or exerting an isometric force); (2) the functional aspects of the same kind of motor output (e.g., static vs. dynamic isometric force; precision vs. power grip); (3) the conditional requirements in the generation of movement (e.g., imposed delays to withhold the movement until a go signal is given); (4) more complex manipulations (e.g., memorized delays), or (5) imposed transformations of an intended movement (e.g., moving at an angle from a stimulus direction).

Static Force

In the original and later work of Evarts, and in subsequent work by others (reviewed in Porter and Lemon, 1993), the force exerted by the animal was restricted to one joint and to the activation of reciprocal groups of muscles. In these experiments, the steady-state activity of a number of motor cortical cells varied with the level of force exerted. The neural relations to static force were extended to the direction of multijoint, two-dimensional (Kalaska et al., 1989), and three-dimensional (Taira et al., 1996) static forces. Cellular activity in the motor cortex varies with and is broadly tuned to the direction of force.

Precision Grip

The original use of precision grip as an experimental tool (Smith et al., 1975) was in accord with the idea that the motor cortex may be particularly involved in the control of precise forces. A precision grip involves the simultaneous activation of a large number of muscles (Smith, 1981; Maier et al., 1990) and, at the same time, an accurate control of force levels as an output motor parameter. Earlier results on the relations between motorcortical cell activity and isometric force in a single joint were interpreted in a simple fashion (Fromm, 1983). For precision grip, however, these relations cannot be interpreted as easily. The desired force levels can be attained by various combinations of muscle activations, and the amount of activation of a particular muscle does not vary in a simple fashion with the amount of force exerted (Maier et al., 1990, 1993). The activity of motor cortical cells is *not* solely or exclusively determined by the motor output; rather, it reflects other processes pertaining to specific aspects of task performance.

The dynamic relations of cellular activity in the motor cortex to the direction of 2-D isometric force pulses were investigated, using an experimental arrangement that dissociated the dynamic and static components of the force exerted (Georgopoulos et al., 1992). Monkeys produced pure force pulses on an isometric handle in the presence of a constant bias force so that the net force (i.e., the vector sum of the monkey's force and the bias force) was in a visually specified direction. The net force developed over time had to stay in the specified direction and to increase in magnitude in order to exceed a required intensity threshold. Now consider the case in which the directions of the net and bias forces differ by being, for example, orthogonal. Under these conditions, the animal's force has to change continuously in direction and magnitude such that, at any moment during

force development, the vector sum of this force and the bias force is in the visually specified direction. This experimental arrangement effectively dissociated the animal's force vector, the direction of which changed continuously in a trial, from the net force vector, whose direction remained invariant. Eight net-force directions and eight bias-force directions were employed. Recordings of neuronal activity in the motor cortex revealed that the activity of single cells was directionally tuned in the absence of bias force and that this tuning remained invariant when the same net forces were produced in the presence of different directions of bias force. These results demonstrated that cell activity does not relate to the direction of the animal's force. Because the net force is equivalent to the dynamic component of the force exerted by the animal, after a static component vector (equal and opposite to the bias force) is subtracted, *these findings suggest that the motor cortex provides the dynamic force signal during force development; other, possibly subcortical, structures might provide the static compensatory signal.* This latter signal could be furnished by antigravity neural systems, given that most static loads encountered are gravitational in nature. According to this general view, the force exerted by the subject consists of dynamic and static components, each of which is controlled by different neural systems. These signals presumably converge in the spinal cord to provide an ongoing integrated signal to the motoneuronal pools.

Locomotion

Single-cell activity in the motor cortex of the locomoting cat is modulated periodically during the stance and swing phases of locomotion (Armstrong and Drew, 1984; Drew, 1993; Beloozerova and Sirota, 1993). However, the amplitude of this periodic modulation was hardly influenced when cats had to locomote uphill, even when the EMG activity increased by approximately 50% (Armstrong and Drew, 1984). This finding led Armstrong and Drew (1984) to question the "central dogma" (p. 492) of that time—namely, that motor cortical activity reflects the magnitude of force exerted or the intensity of activation of target muscles. Instead, the periodicity in cell activity changed with the speed of locomotion, and phase shifts were also observed (Armstrong and Drew, 1984). This finding is in accord with previous findings that motor cortical activity reflects temporal and directional factors probably associated with the selection of muscles to be activated rather than with the intensity of muscle activation.

A clue as to the important determinants of motor cortical activation was obtained by studies involving the locomoting cat in which the cat had to overcome an obstacle (Drew, 1993) or walk in situations that demanded greater precision, such as on the flat rungs of a horizontal ladder (Beloozerova and Sirota, 1993). Such maneuvers produced marked changes in single-cell activity. These observations suggest that the motor cortex is involved when the motor output has to be reorganized into a new pattern, according to the demands of the particular situation. Such reorganization is usually encountered during visuomotor control of the locomoting limbs (Georgopoulos and Grillner, 1989). The role of the motor cortex has thus been shifted from that of a simple *producer* of motor output to a *specifier* of new motor patterns to be produced as a particular condition may demand (Drew, 1993).

Reaching

Reaching is a complex motor pattern involving the concomitant activation of several joints and a larger number of muscles, and yet it is performed gracefully and almost effortlessly. Changes in cell activity were analyzed with respect to a parameter of the reaching movement that captured in a global fashion most of the changes in muscles and joints—namely, its direction in space. A surprisingly orderly relation between the frequency of cell discharge and the direction of reaching was revealed (Georgopoulos et al., 1993). Motor cortical cells are directionally tuned such that their activity varies in a sinusoidal manner with the direction of the movement in space. The tuning curve is broad and covers the entire directional continuum. This means that there is a particular movement direction for which cell activity will be the highest (the "preferred direction" of the cell). Preferred directions differ among cells and are distributed throughout the directional continuum.

Neuronal Population Coding

These findings of cell activity during reaching indicate that the neuronal ensemble engaged with reaching movements consists of directionally tuned cells with diverse directional preferences. The broad tuning of individual cells indicates that a cell will be engaged with movements in many directions. Conversely, many cells will be engaged with movements in a particular direction. Therefore, a unique encoding of the direction of movement may reside within the whole ensemble. This information was extracted by the population vector analysis (Georgopoulos et al., 1983; see also Sparks et al., chapter 2, this volume), which considers a given cell as a vector pointing in its preferred direction and with length

proportional to the intensity of the cell activation. The population vector is the vector sum of the cell vectors and points in the direction of the movement. It is a robust predictor of direction under different postures (Caminiti et al., 1991; Georgopoulos, 1995) and different muscle patterns (Georgopoulos et al., 1992), as well as in various motor areas (Georgopoulos, 1991). In addition, it provides an accurate, time-varying directional signal that can be used to monitor the directional tendency of the neuronal ensemble during the generation, transformation, and selection of motor commands (Georgopoulos et al., 1993).

Finger Movements

The question of coding for and selecting from combinations of finger movements is a basic issue in motor behavior and in motor cortical physiology. Behaviorally, this is an important issue because, during natural manipulation of objects, the fingers are used in groups rather than as isolated entities. Although the ability to move single fingers is, by itself, one of the hallmarks of primate motor behavior, the use of fingers in combinations during object manipulation is the more behaviorally meaningful motor action. In fact, such combinations are being reconfigured dynamically as one manipulates an object in different ways (Schieber and Hibbard, 1993). In their study, Schieber and Hibbard discovered that movements of a particular finger were represented multiply in the motor cortex of the monkey. Conversely, single cells were related to movement of more than one finger. Moreover, neuronal populations active in movements of different fingers overlapped extensively. The authors concluded that "control of any finger movement ... appears to utilize a population of neurons distributed throughout the M1 hand area rather than a somatotopically segregated population" (Schieber and Hibbard, 1993, p. 489). They also remarked (p. 491) on the similarity of this distributed coding of finger movements to the distributed coding of movement direction in reaching, as suggested by Georgopoulos and others (1993).

Instructed Delay Tasks

In an instructed delay task, a sensory stimulus is delivered and a motor response is required *after a period of time*. This task has been used as a probe to identify changes in cell activity during a period in which the information about the upcoming movement has to be retained in the absence of an immediate motor output. Changes in cell activity during an instructed delay period have been observed in practically all precentral motor areas, although they tend to be more common in premotor areas (Tanji and Evarts, 1976; for review, see Wise, 1985; Georgopoulos, 1991; Tanji, 1994). Moreover, the neuronal population vector pointed in the direction of the instructed movement during the delay period (Georgopoulos et al., 1989).

Memorized Delay Tasks

The typical memorized delay task is like the instructed delay task except that the instructing signal is turned off during the delay period. Thus, there is a time period during which information about the upcoming movement has to be kept in memory and used to generate the movement after the go stimulus is given. Several studies have documented changes in cell activity during the memorized delay in motor (Hocherman and Wise, 1991; Smyrnis et al., 1992; Ashe et al., 1993), dorsal premotor (Hocherman and Wise, 1991), and supplementary motor areas (see Tanji, 1994). As in the instructed delay task, the neuronal population vector pointed in the direction of the memorized movement during the memory delay period (Smyrnis et al., 1992).

A study conducted by Alexander and Crutcher (1990a, 1990b) is remarkable because it showed that the direction of movement was dissociated from the pattern of muscle activity within a memorized delay task. The question asked was: Do changes in cell activity during the memorized delay period reflect the muscle pattern or the direction of movement? Three motor areas were studied: the motor cortex, the supplementary motor area, and the putamen. The effect of the intended direction of movement on neural activity was dissociated from the effect of muscle pattern, which was dictated by the applied loads. It was found that (1) many cells in the motor cortex (37%, $n = 202$), the supplementary motor area (55%, $n = 222$), and the putamen (33%, $n = 317$) showed changes in activity during the preparatory period; (2) these changes were selective in anticipation of elbow movements in a particular direction (87% in the motor cortex, 86% in the supplementary motor area, and 78% in the putamen); and (3) these changes were independent of the loading conditions (83% in the motor cortex, 80% in the supplementary motor area, and 84% in the putamen). Alexander and Crutcher concluded, "The near absence of preparatory 'loading effects' in all three motor areas suggests that directional preparatory activity, at least in these structures, may not play a significant role in coding for either the dynamics or the muscle activation patterns of preplanned movements. Instead, such activity may be coding for the intended direction of

movement at a more abstract level of processing (e.g., trajectory and/or kinematics), independent of the forces that the movement will require" (1990a, p. 133).

A study done by Ashe and colleagues (1993) investigated the representation of *memorized trajectories* in the motor cortex. For that purpose, a trajectory with an orthogonal directional bend was used. This task was unique in several respects. First, monkeys had to generate from memory a complex movement trajectory involving a change in direction. Second, the movement was truly internally generated: there was no "go" signal to trigger it. And third, the monkeys were never given a visual signal, either during the recordings or during training, to indicate the endpoint of the movement; therefore, the movement was internally planned. A substantial percentage (62.8%) of cells changed activity during a waiting period preceding the beginning of movement. An interesting observation was that a few cells changed activity *exclusively during the execution of the memorized movement*; these cells were completely inactive during performance of similar movements in the visually guided control task. These findings suggest that *performance of a movement trajectory from memory may involve a specific set of cells*, in addition to the cells activated during both visually guided and memorized movements.

Movement Sequences

When a movement is a simple key press, the complexity of neural responses is more evident in the supplementary motor area than in the motor cortex (Tanji and Kurata, 1985). It seems that the motor cortex is more involved in planning or preparing the motor command when the upcoming movement possesses spatial characteristics (e.g., direction) specified by visuospatial information. Conversely, evidence for a more specific role of the supplementary motor area to memorized sequences of movements was provided recently (Tanji and Shima, 1994).

Transformation of Motor Commands: Mental Rotation of an Intended Movement Direction

The mental rotation task required monkeys to move a handle orthogonally and counterclockwise from a reference direction defined by a visual stimulus in one plane. Because the reference direction changed from trial to trial, the task required that, in a given trial, the direction of movement be specified according to this reference direction (Lurito et al., 1991). When the time-varying neuronal population vector was calculated during the reaction time, it was found that it rotated from the stimulus direction to the movement direction through the counterclockwise angle. It is remarkable that the population vector rotated at all *and* that it rotated through the smaller, 90° counterclockwise angle. The results showed that the cognitive process in this task truly involved rotation of an analog signal. The rotation process, "sweeping" through the directionally tuned ensemble, provided for the first time a direct visualization of a dynamic cognitive process. Interestingly, the rotation rates observed in the neurophysiological studies were very similar to those obtained in psychological studies on human subjects (Georgopoulos and Massey, 1987).

Selection of Motor Commands Based on Context-Recall

The studies done by Lurito and others exemplified the *spatial rule* operating in the mental rotation task, which required the production of a movement at an angle from a stimulus direction. In a different study, Pellizzer and others (1995) sought, instead, to determine the neural correlates of a cognitive process, the rule of which was based not on a spatial constraint, but on the *serial position* of stimuli in a sequence. Given an arbitrary sequence of stimuli on a circle, one of which was identified as the test stimulus, the motor response had to be toward the stimulus that followed the test stimulus in the sequence. When the test stimulus was the first in the sequence, cell activity continued to reflect the direction of the second stimulus, which in this case was the appropriate motor response. However, when the test stimulus was the second in the sequence, neural activity switched abruptly—within approximately 100–150 ms after the "go" signal—to reflect the pattern associated with the direction of the third stimulus, which was now the appropriate motor response. These findings identify the neural correlates of a switching process that is different from a mental rotation task, as described in the previous paragraph. Thus, it seems that the time taken to derive the motor direction in a mental rotation task reflects a transformation, whereas the time taken in a context-recall task reflects a selection process.

Complex Visuomotor Interactions: Inferior Premotor Cortex

The inferior premotor cortex (lateral to the arcuate sulcus) stands apart from other areas by virtue of the presence of complex relations of its cells to visual and motor events. With respect to motor functions, some neurons are activated with proximal arm movements, such as reaching to a goal or bringing the hand to the mouth

(Gentilucci et al., 1988); other neurons with hand movements such as grasping, holding, and tearing (di Pellegrino et al., 1992); and still other neurons with combined reaching-and-grasping actions (Rizzolatti et al., 1990). These functional properties resemble those described in previous studies for area 7 of the posterior parietal cortex (Hyvärinen and Poramen, 1974; Mountcastle et al., 1975). With respect to visual responses, receptive fields are spatially, not retinotopically, organized (Fogassi et al., 1992), and they move with the arm (Graziano et al., 1994).

In summary, visuomotor interaction is clearly an important element in the adaptation of the locomotor movements to the environment, as it is for all reaching, grasping, or pointing movements. During the last decade, the knowledge regarding the neural basis of reaching in three dimensions has markedly expanded. A number of modules in the motor and premotor cortici are involved. Although we know a substantial amount about neuronal processing and population coding in cortex, we are nonetheless left with meager information on cortical level interaction, on the integration between cortical and subcortical motor centers, and on the different mechanisms of spinal-level action. Supraspinal control involves not only the monosynaptic effects on different combinations of target motor neurons, but also effects exerted on different types of interneurons and on spinal neural networks of different types.

Concluding Remarks

In addition to basic propulsive locomotor movements, behaviorally relevant movements require most tetrapods and bipeds to place each foot accurately in each step. In most instances, this accuracy requires a very precise visuomotor coordination, in which the animal strives to modify the limb trajectory in each step, so that the foot lands on an appropriate spot on the ground. In addition, some animals use the foot (with footpads), the fingers, or both to secure attachment to the target structure, a behavior most pronounced in species with arboreal locomotion, such as many primates. They move in the trees or branches and swing themselves between branches, requiring a precise "reaching out" toward the target, as well as a powerful and well-timed grasp. Most likely, not only are many of the cortical systems we have discussed utilized to achieve isolated precise reaching, grasping, and manipulatory movements, but also are used during locomotion (Georgopoulos and Grillner, 1989).

In the first part of this review we dealt with the forebrain and lower brainstem circuitry that initiates and controls the basic locomotor synergy. We considered the role of the basal ganglia in relation to the limbic system and to the lateral and medial hypothalamus. Most of the effects we discussed appear to be channeled via the MLR to the medullary reticulospinal locomotor command. We also evaluated the possibility that the cuneiform nucleus of the MLR is particularly involved in escape reactions, whereas the pedunculopontine part of the MLR might be involved during exploratory behavior and startle reactions involving locomotor activation. During locomotion, which is a part of overall foraging behavior, direct projections from the lateral hypothalamus to the medulla may also be involved. Thus, for the animal in its natural environment, the underlying type of motivation may determine which parts of the forebrain circuitry will be used to initiate a locomotor episode. The different systems will converge, in turn, on the lower brainstem and spinal cord circuitry that generates the basic locomotor synergy. This synergy requires cycle-to-cycle modifications, including visuomotor coordination that involves the motor cortex.

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