Behavioral/Systems/Circuits

Spinal and Supraspinal Control of the Direction of Stepping during Locomotion

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Most bipeds and quadrupeds, in addition to forward walking, are also capable of backward and sideward walking. The direction of walking is determined by the direction of stepping movements of individual limbs in relation to the front-to-rear body axis. Our goal was to assess the functional organization of the system controlling the direction of stepping. Experiments were performed on decerebrate cats walking on the treadmill with their hindlimbs, whereas the head and trunk were rigidly fixed. Different directions of the treadmill motion relative to the body axis were used (0, ±45, ±90, and 180°). For each direction, we compared locomotion evoked from the brainstem (by stimulation of the mesencephalic locomotor region, MLR) with locomotion evoked by epidural stimulation of the spinal cord (SC).

It was found that SC stimulation evoked well coordinated stepping movements at different treadmill directions. The direction of steps was opposite to the treadmill motion, suggesting that this direction was determined by sensory input from the limb during stance. Thus, SC stimulation activates limb controllers, which are able to generate stepping movements in different directions. By contrast, MLR stimulation evoked well coordinated stepping movements only if the treadmill was moving in the front-to-rear direction. One can conclude that supraspinal commands (caused by MLR stimulation) select one of the numerous forms of operation of the spinal limb controllers, namely, the forward walking. The MLR can thus be considered as a command center for forward locomotion, which is the main form of progression in bipeds and quadrupeds.

Introduction

In vertebrates, nervous mechanisms at different levels of the CNS participate in the control of locomotion. Stepping movements of individual limbs are generated by spinal neuronal circuits (limb controllers; Orlovsky et al., 1999). Supraspinal centers activate these spinal mechanisms and adapt their activity to different behavioral tasks and environmental conditions (for review, see Sherrington, 1906; Grillner, 1975; Shik and Orlovsky, 1976; Arshavsky et al., 1986).

One important task of the locomotor system is the control of the direction of stepping movements of individual limbs relative to the front-to-rear body axis. Most bipeds and quadrupeds, in addition to the main form of locomotion, forward walking, are also capable of backward and sideward walking (Stein et al., 1986;

Buford and Smith, 1990; Buford et al., 1990; Rossignol, 1996; Deliagina et al., 1997; Zelenin et al., 2011). Also, the steps deviated from the direction of progression are used for correcting perturbations of balance during forward walking (Karayannidou et al., 2009; Musienko et al., 2012). Steps with a lateral component can also be initiated by large postural perturbations during standing (Karayannidou et al., 2009). The mechanisms controlling the step direction are mostly unknown. A goal of the present study was to assess functional organization of the system controlling the direction of stepping, as well as the role of different CNS levels in this control. For this purpose, we compared locomotion of decerebrate cats evoked by stimulation of the brainstem and by stimulation of the spinal cord (SC).

It is known that electrical stimulation of the mesencephalic locomotor region (MLR) evokes locomotion in the decerebrate cat (Shik et al., 1966; Shik and Orlovsky, 1976; Jordan, 1986; Garcia-Rill and Skinner, 1987a,b). This stimulation activates locomotor mechanisms of the brainstem and SC (for review, see Arshavsky et al., 1986). Locomotion in the decerebrate cat can also be evoked by epidural electrical SC stimulation near its dorsal midline (Iwahara et al., 1992; Musienko et al., 2007, 2012). SC stimulation also evokes locomotion in spinal subjects (Gerasimenko et al., 2003), and it was suggested that it activates spinal mechanisms of stepping (limb controllers; Orlovsky et al., 1999) through the afferents of the dorsal roots (Gerasimenko et al., 2005). Thus, one can suggest that SC stimulation in the decerebrate cat primarily activates the spinal limb controllers, and much less affects the supraspinal mechanisms.

In the present study, we compared MLR- and SC-evoked locomotion on the treadmill moving in different directions. We have found that at any direction of the treadmill, SC stimulation evoked well coordinated stepping movements opposite to the treadmill motion. In contrast, MLR stimulation evoked coordinated stepping movements only when the treadmill was moving backward. These findings suggest that SC stimulation activates limb controllers, and they generate stepping movements in different directions on the basis of sensory input coming from the limb during stance. In contrast, MLR activates only one of the numerous forms of operation of the spinal limb controllers, namely, the forward walking.

A brief account of this study was published in abstract form (Deliagina et al., 2012).

Materials and Methods

Subjects. Experiments were performed on nine adult cats of either sex (weighting 2.2– 4.0 kg). All procedures were conducted according to the European Community Council Directive (November 24, 1986, 86/609/ EEC) in accordance with a protocol approved by the Animal Care Committee of the Pavlov Institute of Physiology, St. Petersburg, Russia, and followed the guidelines of the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Surgical procedures. The cats were anesthetized deeply with a mixture of xylazine (1 mg/kg, i.m.) and ketamine (40 mg/kg, i.m.), and supplemented 30–50% of the initial dose if necessary. The level of anesthesia was monitored based on applying pressure to the paw (to detect limb withdrawal), as well as by checking the size and reactivity of the pupils. The trachea was cannulated and carotid arteries were ligated. The animal was decerebrated at the precollicular-postmammilar level. A laminectomy was performed in the lumbar area. Bipolar electromyographic (EMG) electrodes (0.2 mm flexible stainless steel Teflon-insulated wires) were implanted bilaterally into the gastrocnemius lateralis (Gast; ankle extensor), tibialis (Tib; ankle flexor), adductor femoris (Add; hip extensor and adductor), and gluteus medius (Glut; hip extensor and abductor) as described previously (Gerasimenko et al., 2009). Our reason for recording these particular muscles was that Gast and Tib take part in the longitudinal component of step, while Glut and Add also take part in the lateral component of step. Anesthesia was discontinued after the surgical procedures, and the experiments were initiated 2–3 h thereafter.

During the experiment, the rectal temperature and mean blood pressure of the animal were continuously monitored and were kept at 37 ± 0.5°C and >80 mmHg.

Experimental design. The experimental design is shown in Figure 1. The head of the decerebrate animal, the vertebral column, and the pelvis were fixed in a rigid frame (Fig. 1A), ensure straight trunk configuration. Such trunk configuration is similar to that observed in intact cats during forward walking, but differs from that assumed by animals during backward walking (Buford et al., 1990). However, for standardization of conditions for comparison, we provided equal "posture" for all locomotor tests. There was no support surface under the forelimbs. During evoked locomotion of the hindlimbs, the forelimbs usually did not move rhythmically or performed weak stepping movements in the air. The hindlimbs were positioned on the treadmill with two separate belts (left and right) moving at the same speed (0.5 m/s) and referred to below as "treadmill belt." The distance between the treadmill belt and the fixed pelvis was 21–25 cm (depending on the animal size), which determined a hemiflexed limb configuration in the middle of stance typical for walking. The treadmill could be oriented at different angles (α) relative to the longitudinal body axis; six values of α were used: 0°, 45°R, 45°L, 90°R, 90°L, and 180°. For each orientation, the treadmill velocity vector is indicated by arrow in Figure 1B. In addition, we tested the ability of the cat to perform stepping in place on the stopped treadmill and in air (with no support surface under the hindlimbs).

Locomotion was evoked by stimulating either MLR or SC. The stimulation started in 2–3 s after onset of the treadmill belt motion. We used parameters of stimulation that were found optimal in the previous stud-

ies (Shik et al., 1966; Musienko et al., 2007, 2012). For MLR stimulation, a bipolar electrode (two 150 μm wires insulated except for the tips and separated by 0.5 mm) was inserted into the brainstem area (Horsly–Clark coordinates P2, R/L4, H0) by means of a micromanipulator (Fig. 1A, MLR-stim). We used the following parameters of stimulation: frequency, 30 pulses per second (pps); pulse duration, 0.5–1 ms; and current, 50– 200 μA. For epidural SC stimulation, a ball electrode ($d = 0.5$ mm) was positioned on the dura mater in the middle of the dorsal surface of the spinal cord at the L5 level (Fig. 1A, SC-stim). We used the following parameters of stimulation: frequency, 5 Hz; pulse duration, 0.2–0.5 ms; and current, 100–300 μA.

In each locomotor test, the rear view and the side view of the walking cat were recorded by two video cameras (25 frames/s), which were synchronized with EMG recordings. In addition, in the tests with forward and backward walking, we recorded the anterior–posterior (A-P) limb movements (by means of two mechanical sensors, one of which, Limb-R, is shown in Fig. 1A), as well as the vertical forces developed by each of the limbs (by means of two force plates positioned under the left and right moving belts; Fig. 1A, FP).

Data analysis. The signals from the EMG electrodes and from the position sensors were amplified, digitized with a sampling frequency of 5 (EMGs) and 1 kHz (sensors), and recorded on a computer disk using the data-acquisition and analysis software (Power-1401/Spike2; Cambridge Electronic Design). The EMGs were rectified (see Fig. 2, A,B). During locomotion evoked by SC stimulation, the EMG signals contained large responses to each stimulating pulse (coming at 5 pps; Figs. 2B, 8B,D,F, 9D). These responses were removed during analysis with a custom-written program triggered by stimulating pulses. The EMG signals were then averaged for each of the 100 bins of the step cycle that was normalized to 1.0 (over a sequence of 5–20 steps). The beginning of the swing phase was taken as the cycle onset.

The video recordings were analyzed frame by frame. From the rear view (Fig. 1A, Video-1) and/or from the side view (Fig. 1C, Video-2) it was easy to establish whether the foot was on the ground (i.e., the limb was in the stance phase of its step cycle) or the foot was lifted (i.e., the limb was in the swing phase). During the stance phase, the vertical foot coordinate $Z = 0$ and the foot trajectory could be entirely characterized by two coordinates, X and Y (Fig. 1C). A grid of coordinates (that compensated for distortions of perspective) was applied to the image of the treadmill area (Fig. 1C). Using this grid, foot coordinates were measured in sequential frames. If there were no displacements of the foot in relation to the moving belt, the foot trajectory throughout the stance would be a straight line parallel to the velocity vector (Fig. 1C, thick gray line), with equal interpoint distances. We considered such results as evidence that the step was adapted to the treadmill motion. If there were foot displacements during the stance, the foot trajectory would deviate from the treadmill belt velocity vector, indicating that the step was not adapted to the treadmill motion. To estimate quantitatively the deviation of the foot trajectory from the velocity vector, for each step we determined "approximated stance trajectory" (the line connecting the initial and final stance positions), and then calculated the angle between this line and the velocity vector (S-V angle).

During the swing phase, the foot was lifted above the ground, but its vertical coordinate Z could not be precisely measured with our methods. Therefore, the foot trajectory during swing could be characterized only roughly in X/Y coordinates.

All quantitative data in this study are presented as mean ± SD. Student's t test was used to characterize the statistical significance when comparing different means; the significance level was set at $p = 0.05$.

Results

Only the cats exhibiting well coordinated forward walking on backward moving treadmill during MLR stimulation and/or SC stimulation were tested under other conditions using the parameters of stimulation that were effective for forward walking. In two animals (cat 2 and cat 4), walking at different conditions was examined during MLR-evoked locomotion and SC-evoked locomotion of the same vigor (i.e., with similar values of contact forces and EMG amplitudes). In other cats, the quality of walking was better with one of the stimulation sites; correspondingly, in

two cats, only MLR-evoked locomotion was investigated, and in five other cats, we tested only SC-evoked locomotion. The data obtained from cat 4 will be used to illustrate locomotion in different directions evoked by MLR and SC stimulation.

Treadmill angle 0°
MLR and SC stimulation
Forward walking (treadmill angle $\alpha = 0°$, Fig. 1B) of cat 4 evoked by MLR stimulation is illustrated in Figure 2A, and that evoked by SC stimulation in Figure 2B. The two locomotor patterns were mostly similar. In both cases, stepping limb movements were rather uniform, with the step cycle duration of 0.7–0.8 s, the peak contact force ~ 0.7 kg, and similar step length. The right and left limbs were stepping in antiphase.

The EMG patterns were also similar in these two tests: the muscles with extensor function (Gast, Add, Glut) were active during the stance phase of the limb, and the flexor (Tib) was active during the swing phase. The EMG signals during SC-evoked locomotion contained large short-latency responses to stimulating pulses, coming at a frequency of 5 pps (Figs. 2B; Fig. 8B,D,F, 9D). Figure 7 (0°) shows averaged EMGs during MLR-evoked (A) and SC-evoked (B) forward walking. One can see that the EMG patterns were mostly similar.

Figure 3A shows a trajectory of the right foot in X/Y coordinates (Fig. 1C) during one step cycle of forward walking evoked by MLR stimulation. In the stance phase (filled circles, 1–11), the foot moved from the extreme front position to the extreme rear position along a straight trajectory, in parallel both to the velocity vector (large black arrow) and to the body axis (thick gray line), at the speed equal to that of the treadmill. In the swing phase, the foot rapidly returned to the extreme front position (empty circles, 12–18).

To evaluate variability of stepping limb movements in sequential steps, we approximated the stance trajectory by a straight line connecting the initial and final stance positions. Figure 3B shows the approximated stance trajectories for 10 sequential steps of the right limb; the orthogonal bars indicate double SD values for X and Y coordinates, at the initial and final stance positions. In each trajectory, the Y value at these two positions was the same, indicating that the trajectories were parallel to the velocity vector and to the body axis; the mean value of the S-V angle in cat 4 was 0° (red interrupted line). Stance trajectories of the left limb were also parallel to the velocity vector (one of these trajectories is shown in Fig. 3A). Similar results were obtained in all tested cats (Fig. 4, bar 1; Table 1, column 0°). Figure 3, C and D, illustrates forward walking in cat 4 evoked by SC stimulation. Again, stance trajectories were found to be parallel to the velocity vector. Similar results were obtained in all tested cats: the mean value of the S-V angle was 0° (Fig. 4, bar 2; Table 1, column 0°).

The alignment of the stance trajectory and the velocity vector during both MLR-evoked and SC-evoked forward walking suggested that the foot contacted the same spot on the moving tread-
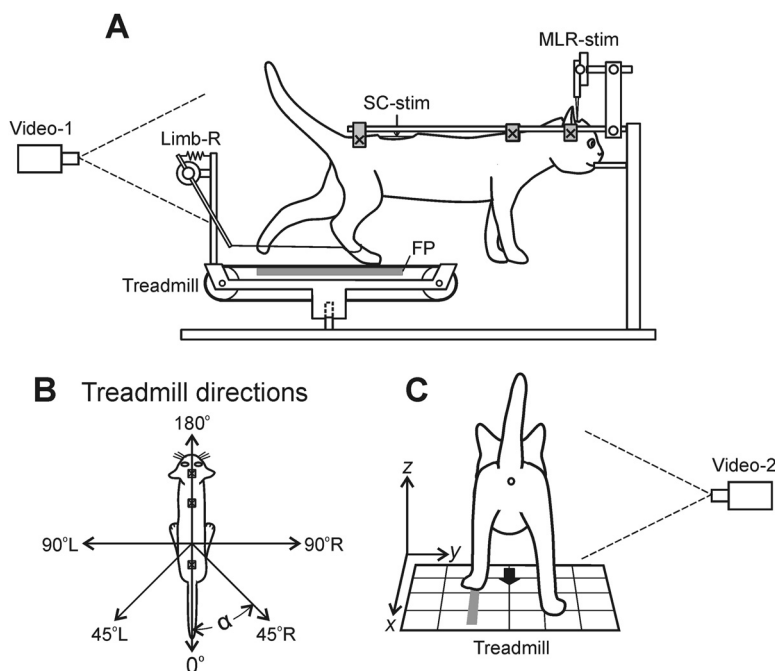

Figure 1. Experimental design. *A*, The head, vertebral column, and pelvis of a decerebrate cat were fixed in a rigid frame (points of fixation are indicated by X). The hindlimbs were positioned on the treadmill. Walking of the hindlimbs was evoked by stimulation of the MLR (MLR-stim) or the SC (SC-stim). A-P movements of each limb were recorded by a sensor (only the right sensor, Limb-R, is shown). The contact force under each limb (during forward and backward walking) was measured by a force plate (FP). *B*, The treadmill could be oriented differently relative to the longitudinal body axis (angle α); for each orientation, the treadmill velocity vector is indicated by an arrow. *C*, The coordinate system (*X, Y,Z*) used for the movement analysis; the *X, Y* grid was applied to the image of treadmill area to determine foot position in sequential frames. The limb stepping was considered as adapted to the belt movement if the stance trajectory (gray line) was parallel to the velocity vector (large arrow). The rear view and the side view of the walking cat were recorded by two video cameras (Video-1 in *A*, and Video-2 in *C*, respectively).

mill belt throughout the stance phase. For this reason, we considered the forward walking as a form of locomotion well adapted to the treadmill motion.

Treadmill angle 90°
MLR stimulation
The MLR-evoked locomotion on the treadmill moving sideward in cat 4 had some characteristics similar to those of forward walking in this cat: the step cycle duration was 0.7–0.9 s, and steps of opposite limbs alternated. The step length in the leading (performing outward step) limb was slightly larger than in trailing (performing inward step) limb (17.9 ± 3.0 cm against 16.1 ± 3.1 cm, respectively). Large variability of the step direction and amplitude was observed. The limbs frequently collided with each other, causing additional distortion in their stepping.

Figure 5A shows the trajectory of the left foot during one step cycle of walking on the treadmill positioned at $\alpha = 90°R$. In the stance phase, the foot moved from the initial stance position (point 1) rightward at the velocity of the treadmill motion (points 1–5), suggesting that this movement was caused by the moving treadmill belt. The foot decelerated (points 5–8) and then started moving backward despite the rightward motion of the treadmill (points 8–16), suggesting that this movement was caused by active contraction of limb muscles. After reaching the final stance position (point 16), the swing phase began, and the foot rapidly returned to its initial position (point 22). The shape of stance trajectory in different cycles was highly variable, from the two-section shape (with one section parallel to the treadmill velocity vector, and another one parallel to the trunk axis, as illustrated in Fig. 5A), to the one-section shape trajectory laying between the
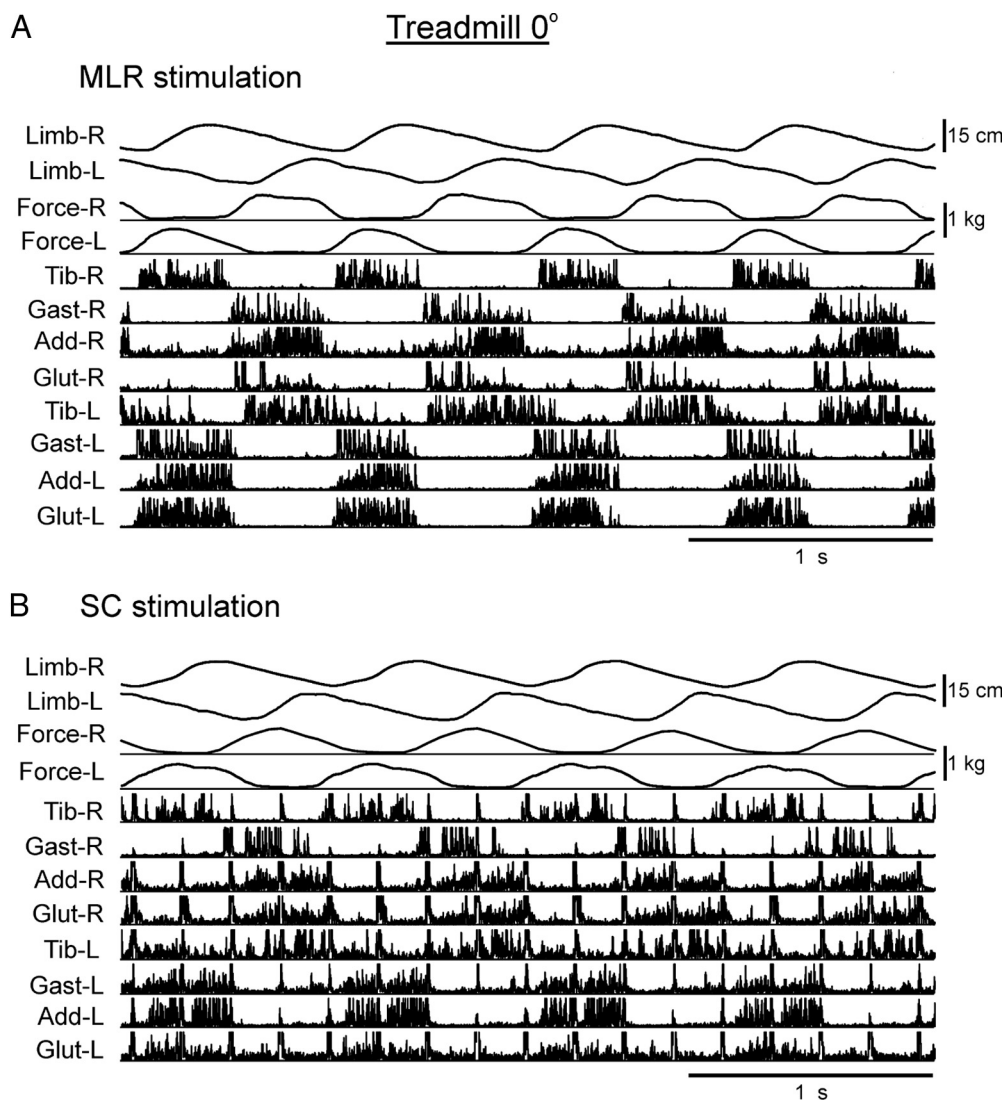
Figure 2. Forward locomotion in cat 4 (treadmill angle $\alpha = 0°$) evoked by MLR stimulation (*A*) and SC stimulation (*B*). Recording of movements of the right and left limbs (Limb-R and Limb-L), contact forces (Force-R and Force-L), and EMGs.

trunk axis and treadmill velocity vector (illustrated in Fig. 6A). Figure 5B shows the approximated stance trajectories (see Materials and Methods) for 10 sequential steps of the left limb; the orthogonal bars indicate double SD values for X and Y coordinates at the initial and final stance positions. One can see a large variability of these trajectories. All trajectories were considerably inclined in relation to the velocity vector. The mean angle of the stance trajectory in cat 4 was 40 ± 15° (red interrupted line). Similar results were obtained in all tested cats: the mean value of the S-V angle was 39 ± 14° (Fig. 4, bar 5; Table 1, column 90°). This finding suggests that, during the stance phase, the foot contacted different spots on the moving treadmill belt, i.e., the limb was sliding on the support surface because the direction of active foot movement differed from that of support surface movement. For this reason, we considered MLR-evoked walking as a form of locomotion poorly adapted to the sideward treadmill motion (Table 1, column 90°). It seems likely that the limb controllers generated the motor pattern of forward walking rather than the pattern of sideward walking, which caused dramatic distortions of stepping movements (see Discussion).

SC stimulation

The SC-evoked walking on the treadmill moving sideward in cat 4 had some characteristics similar to those in the MLR-evoked walking: the step cycle duration was 0.7–0.8 s, steps of the opposite limbs alternated, and limb movements were asymmetrical, with longer steps in the leading limb (14.0 ± 1.4 cm) and shorter in trailing limb (10.2 ± 0.8 cm). Also, the stepping limbs could collide with each other. However, the locomotor limb movements with SC stimulation were much more consistent than with MLR stimulation.

Figure 5C shows a trajectory of the left foot during one step cycle of SC-evoked locomotion on the rightward moving treadmill. In the stance phase (points 1–11), the foot moved rightward from the initial stance position (point 1) to the final stance position (point 11) along a straight trajectory, in parallel to the velocity vector and perpendicular to the body axis, at the velocity equal to that of the treadmill. In the swing phase, the foot rapidly returned to the extreme front position (points 12–20). In addition, Figure 5C shows an approximated stance trajectory of the right foot, which was also parallel to the velocity vector. It is important to note that there was some distance (~7 cm) between the stance trajectories of the right and left feet. Due to this distance, the left limb performed its lateral steps in

the more rostral position than the right limb (Fig. 5E), which helped the limbs to reduce collisions with each other.

Figure 5F shows extreme positions of the leading (left) and trailing (right) limbs in the stance phase (in X-Z coordinates). One can see a significant asymmetry in stepping movements of the two limbs.

Figure 5D shows 10 approximated stance trajectories of the left foot (cat 4) during SC-evoked walking on the rightward moving treadmill. The variability of trajectories was much smaller than in the MLR-evoked walking (Fig. 5B). All stance trajectories were parallel to the velocity vector; the mean value of the S-V angle in cat 4 was 0° (red interrupted line). Similar results were obtained in all tested cats (Fig. 4, bar 6; Table 1, column 90°). On this reason, one can conclude that the SC-evoked locomotion was well adapted to the sideward treadmill motion, and can be termed the sideward walking. A striking difference between MLR- and SC-evoked walking was also manifested in different EMG patterns (see below).

Treadmill angle 45°

MLR stimulation

Most characteristics of MLR-evoked walking in cat 4 on the treadmill positioned at $\alpha = 45°$ were similar to those obtained at $\alpha = 90°$: the step cycle duration was 0.7–0.8 s, steps of the opposite limbs alternated, and limb movements were symmetrical (the step amplitude was 17.0 ± 3.1 cm in the leading limb against 16.8 ± 1.93 cm in the trailing limb). A large variability of the step direction and amplitude was also observed. The limbs frequently collided with each other, causing disruption in their stepping.

Figure 6A shows an example of the left foot trajectory during one step cycle of cat 4 (treadmill angle $\alpha = 45°$R). In the stance phase, the foot moved from the extreme front position (point 1) to the extreme rear position (point 15) along an almost rectilinear trajectory. The angle of this trajectory relative to the body axis was 24°, i.e., it was between the trunk angle (0°) and the treadmill angle (45°). The foot movement along the trajectory was uneven, with an increased velocity in the middle of stance. In the swing phase, the foot moved from the extreme rear position (point 15) to the extreme front position (point 22), which was close to the starting position (point 1).

The shape of stance trajectories at the treadmill angle $\alpha = 45°$ was as variable as at $\alpha = 90°$. Figure 6B shows the approximated stance trajectories for 10 sequential steps of the left limb. One can see a large variability of stance trajectories. All individual trajectories were inclined in relation to the velocity vector. The mean angle of the stance trajectory relative to this vector in cat 4 was $21 \pm 5°$ (red interrupted line). Similar results were obtained in all tested cats: the mean value of the S-V angle was $17 \pm 6°$ (Fig. 4, bar 3; Table 1, column 45°).
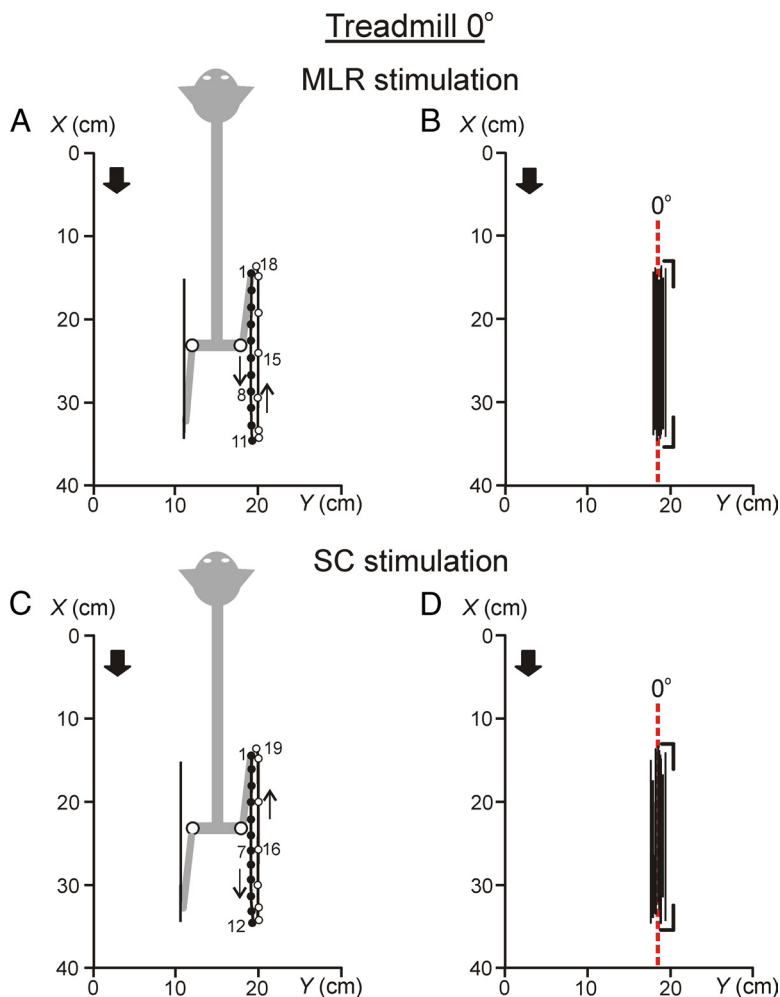

Figure 3. Forward locomotion in cat 4 (treadmill angle $\alpha = 0°$) evoked by MLR stimulation (**A, B**) and SC stimulation (**C, D**). **A, C**, Sequential positions (40 ms between frames) of the right foot during one step cycle. **B, D**, Approximated stance trajectories in 10 sequential step cycles of the right limb. The mean value of the S-V angles (between approximated stance trajectory and velocity vector) is shown by the red interrupted line. The orthogonal bars indicate double SD values for X and Y coordinates, at the initial and final stance positions. Position of the cat's head, trunk, pelvis, and limbs relative to the treadmill area is indicated. The large arrow designates the belt velocity vector. Symbols: filled circles, stance; empty circles, swing.
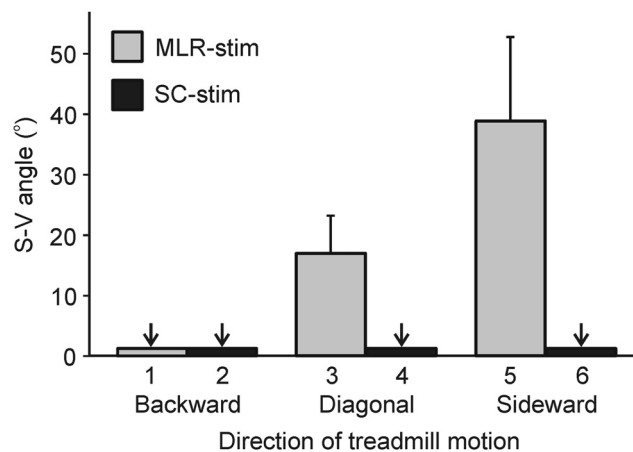

Figure 4. Characteristics of stance trajectory during MLR- and SC-evoked locomotion. The mean value ($\pm$SD) of S-V angles is shown for the backward ($\alpha = 0°$), diagonal ($\alpha = 45°$), and sideward ($\alpha = 90°$) direction of treadmill motion. The data for 45°R and 45°L, as well as for 90°R and 90°L, were pooled together. In bars indicated by arrows, this angle was close to zero (within measurement errors). Number of animals and data points in each average (bars 1– 6) were as follows: 1, 4 and 138; 2, 7 and 102; 3, 3 and 160; 4, 4 and 83; 5, 3 and 156; and 6, 4 and 90.

Table 1. Proportion of animals with walking adapted to different directions of treadmill motion

Stimulation	Treadmill direction			
	0°	45°	90°	180°
MLR	100% (4/4)	0% (0/3)	0% (0/3)	0% (0/4)
SC	100% (7/7)	100% (4/4)	100% (4/4)	57% (4/7)

A cat was considered as adapted to a given treadmill direction if it was walking, and the mean value of the S-V angle was less than 5°.
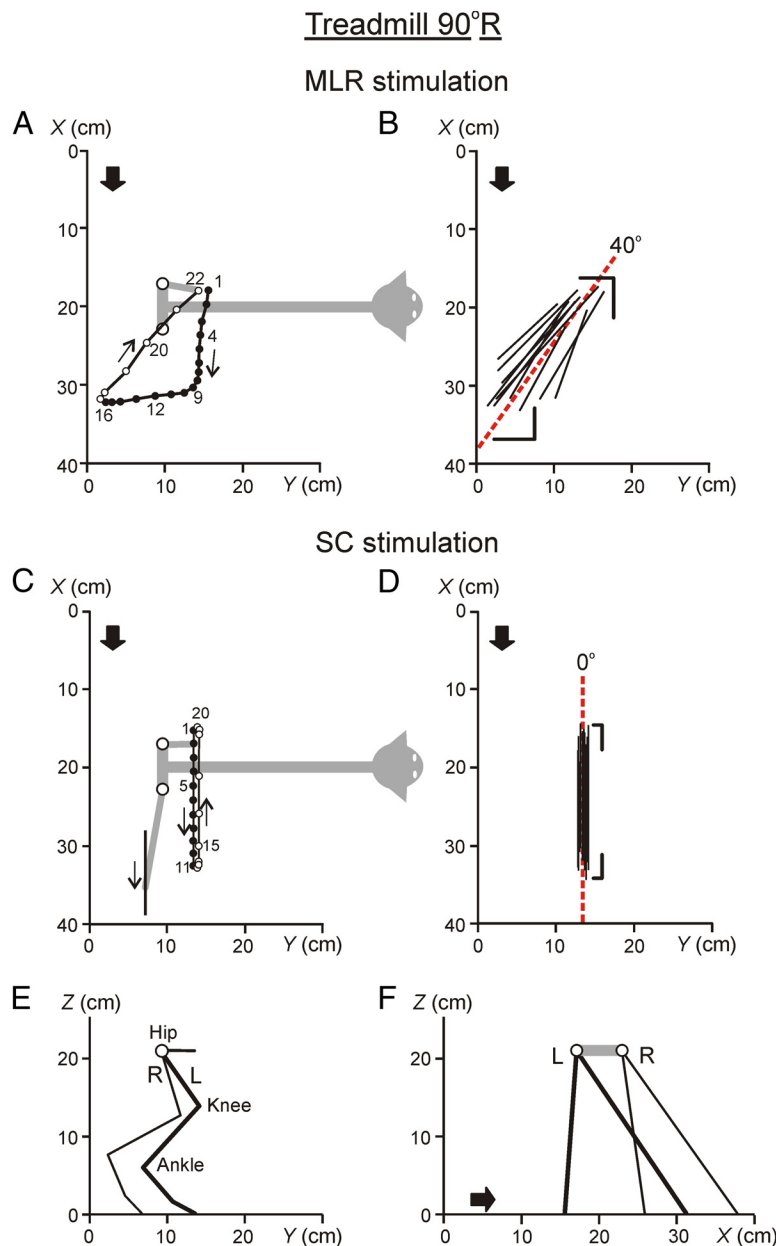
Treadmill 90°R

MLR stimulation

SC stimulation

Figure 5. Locomotion evoked by MLR stimulation (*A*, *B*) and SC stimulation (*C*, *D*) in cat 4 on the treadmill moving sideward (α = 90°R). *A*, *C*, Sequential positions of the left foot during one step cycle. In *C*, the approximated stance trajectory of the right foot is also shown. *B*, *D*, Approximated stance trajectories in 10 sequential step cycles of the left limb, as well as the mean value of their S-V angles (red interrupted line). *E*, Configuration of the left (L) and right (R) limbs in the mid-stance (in *Y-Z* coordinates). *F*, Extreme positions of the L and R limbs in the stance phase (in *X-Z* coordinates). Leading and trailing limbs (performing outward and inward step, respectively) are shown by thick and thin lines, respectively. Symbols and designations as in Figure 3.

These data show that, during the stance phase, the foot was sliding on the support surface. For this reason, one can conclude that MLR-evoked walking was poorly adapted to the treadmill motion (Table 1, column 45°).

SC stimulation

The SC-evoked walking on the treadmill positioned at α = 45° in cat 4 was in some respects similar to that evoked by MLR stimulation: the step cycle duration was 0.7–0.8 s, steps of the opposite limbs alternated, and limb movements were asymmetrical, with longer steps in the leading limb (15.5 ± 1.0 cm) and shorter in the trailing limb (10.7 ± 0.9 cm). Also, the stepping limbs could collide with each other. However, the motor pattern was much more consistent with SC stimulation than with MLR stimulation, as it was also shown for SC-evoked sideward walking (see above).

Figure 6, *C* and *D*, shows the trajectory of the left foot in one of the steps (*C*) and 10 approximated stance trajectories (*D*) of cat 4 (treadmill angle α = 45°R). The variability of trajectories was much smaller than in the MLR-evoked walking (Fig. 6*B*). All stance trajectories were parallel to the velocity vector; the mean angle of the stance trajectory in cat 4 was 0° (red interrupted line). Similar results were obtained in all tested cats (Fig. 4, bar 4; Table 1, column 45°).

Again, as with 90°, one can conclude that the SC-evoked locomotion was well adapted to the treadmill motion at 45°, and can be termed the diagonal walking. A striking difference between MLR- and SC-evoked walking was also reflected in different EMG patterns (see below).

Comparison of EMG patterns of MLR- and SC-evoked locomotion at treadmill angles 0, 45, and 90°

Figure 7 shows an average activity in four muscles of the right limb as a function of the step phase (see Materials and Methods). Recordings were performed in five tests with different treadmill direction (cat 4). Locomotion was evoked by MLR stimulation (*A*) and SC stimulation (*B*). The structure of locomotor cycle during forward walking (treadmill angle 0°) evoked by MLR and SC stimulation was similar: the swing terminated at phase 0.35–0.38. In both MLR- and SC-evoked walking at treadmill angles 45 and 90°, the structure of the cycle in leading and trailing limbs was different. The swing was longer (up to 0.54) in the trailing limb (Fig. 7*A*, *B*, 45°R, 90°R), and shorter (down to 0.25) in the leading limb (Fig. 7*A*, *B*, 90°L). These changes in cycle structure were most likely caused by limb collisions. Similar results were obtained in all eight tested cats.

MLR stimulation

From Figure 7*A* one can see that phasing of individual muscles in the step cycle only weakly depended on the direction of treadmill motion: the EMG burst of Tib-R was timed to the swing phase of

the right limb, whereas the EMG bursts of Gast-R, Glut-R, and Add-R were mostly confined to the stance phase. In contrast, the magnitude of EMG activity depended on the treadmill direction, especially in Glut-R, in which it was much larger with the limb leading ($\alpha = 45°$L and 90°L) than with the limb trailing ($\alpha = 45°$R and 90°R). A similar but weaker dependence was observed in Add-R. Similar EMG patterns were observed in the other three cats with MLR-evoked locomotion.

SC stimulation

Figure 7B shows average EMG activity during SC-evoked locomotion. The EMG waveforms during forward walking ($\alpha = 0°$) were basically similar to those during MLR-evoked locomotion (Fig. 7A): the EMG burst of Tib-R was timed to the swing phase of the right limb, whereas the EMG bursts of Gast-R, Glut-R, and Add-R were mostly confined to its stance phase. However, the EMG waveforms during walking in other directions differed markedly from those during MLR-evoked locomotion. The main difference was that the activity of muscles during SC-evoked locomotion was much less confined to a definite phase of the step cycle. For example, Tib-R was active mainly during swing of the right limb at $\alpha = 0°$ and 45°L, in the end of swing and beginning of stance at $\alpha = 90°$L, and at the end of swing and during stance at $\alpha = 45°$R, 90°R. Similarly, Gast-R had a peak in the early stance at $\alpha = 0°$, 45°L, 45°R, and 90°L, but it was active in the late stance and early swing at $\alpha = 90°$R. Glut-R was

active in stance at $\alpha = 0°$, 45°L, and 90°L, but it was active in swing at $\alpha = 45°$R and 90°R. One can also see that the treadmill direction affected the EMG magnitude (e.g., in Glut-R, Gast-R). The EMG patterns in other cats ($N = 4$) were basically similar to that in cat 4, though some differences in the peak EMG and its phasing could be found.

To summarize, during MLR-evoked locomotion, the EMG patterns for all directions of walking were basically similar to those of forward walking. During diagonal and sideward treadmill motion, these EMG patterns resulted in limb movements that were not aligned to the treadmill direction. In contrast, during SC-evoked locomotion, limb movements were aligned to the direction of treadmill motion. This was caused by considerable modifications of EMG patterns compared with forward walking.

Backward, in-place, and air stepping

Figure 8A shows an example of the effects of MLR stimulation under different support conditions in cat 5. Initially, the treadmill was moving backward ($\alpha = 0°$), and the cat was walking forward. Then the treadmill was stopped, and stepping movements discontinued. Then the treadmill started moving forward ($\alpha = 180°$), and stepping movements were absent. Finally, the treadmill started moving backward ($\alpha = 0°$), and forward walking
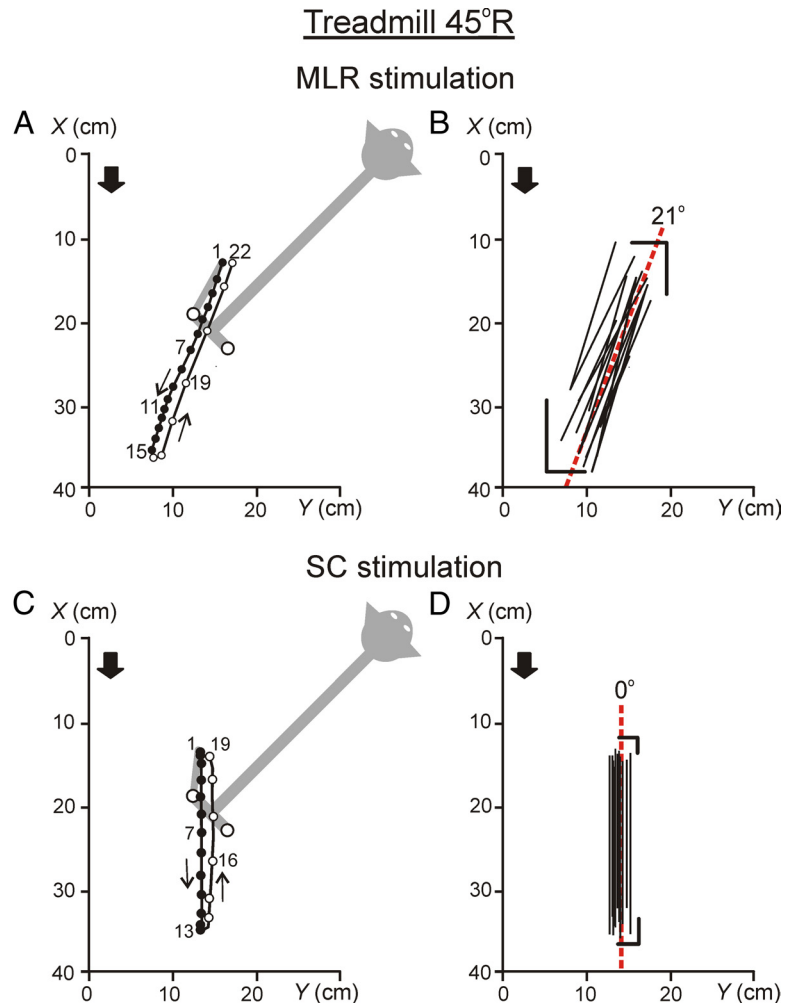

Figure 6. Locomotion evoked by MLR stimulation (**A**, **B**) and SC stimulation (**C**, **D**) in cat 4 on the treadmill moving at $\alpha = 45°$R. **A**, **C**, Sequential positions of the left foot during one step cycle. **B**, **D**, Approximated stance trajectories in 10 sequential step cycles of the left limb, as well as the mean value of their S-V angles (red interrupted line). Symbols and designations as in Figure 3.

resumed. With MLR stimulation, neither backward walking (at $\alpha = 180°$) nor in-place stepping were observed in any of four tested cats.

Figure 8, B–G, shows the effects of SC stimulation under the same support conditions in cat 2. Like MLR stimulation (Fig. 8A), SC stimulation evoked forward walking ($\alpha = 0°$; Fig. 8B,C). Unlike MLR stimulation, however, SC stimulation evoked backward walking ($\alpha = 180°$; Fig. 8D,E). Stepping limb movements were rather uniform, with the step cycle duration of 0.6–0.7 s, the step length 7–11 cm, i.e., much smaller than during forward walking. The peak contact force (0.3–0.5 kg) was also smaller than during forward walking. The right and left limbs were stepping in antiphase. These characteristics of backward locomotor pattern were similar to those described earlier for intact (Buford and Smith, 1990; Buford et al., 1990; Zelenin et al., 2011) and decerebrate cats (Musienko et al., 2007).

Figure 8E shows a side view of the left foot trajectory during one step cycle of backward walking. In the stance phase (filled circles, 1–7), the foot moved from the extreme posterior position to the extreme anterior position. In the swing phase, the foot rapidly returned to the extreme posterior position (empty circles, 7–15). One can see that the limb locomotor movements were performed in much more rostral position in relation to the body
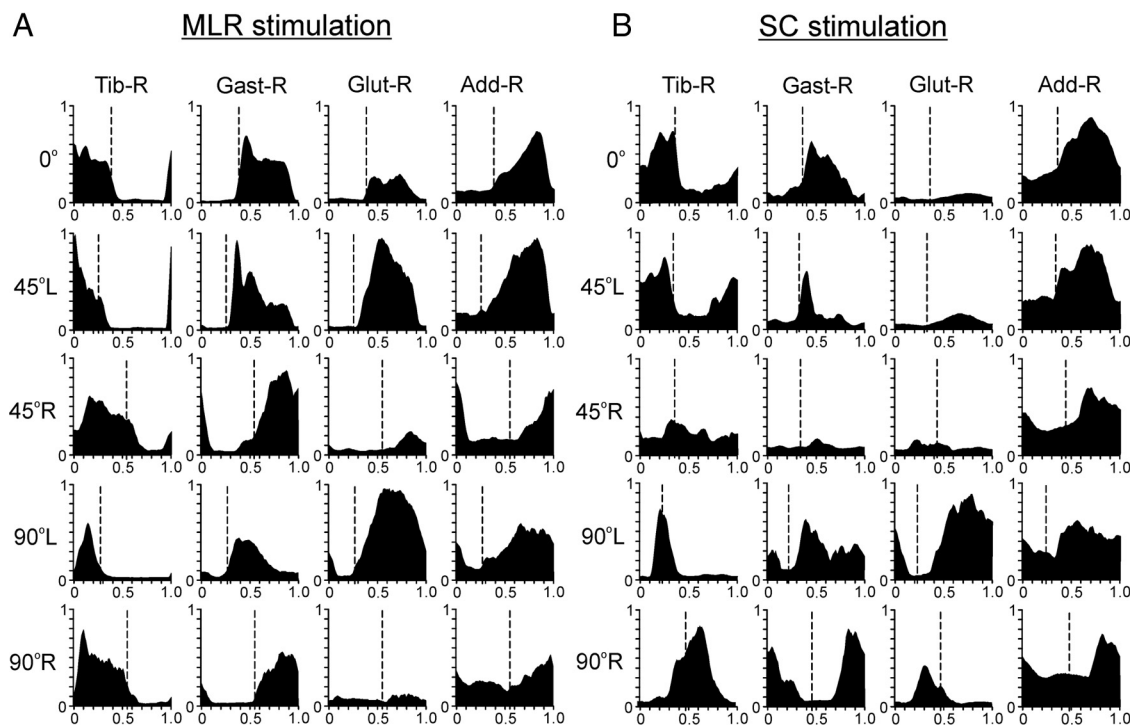
Figure 7. EMG patterns of MLR-evoked (**A**) and SC-evoked locomotion (**B**) in cat 4 at treadmill angles 0, 45, and 90°. At each treadmill angle, EMGs of the right limb muscles were averaged over 10 sequential step cycles. The step cycle was normalized to 1.0; the beginning of the swing phase was taken as the cycle onset and the swing termination is indicated by an interrupted line. Abscissa: phase of step cycle; ordinate: EMG (A.U.).

compared with movements during forward walking (Fig. 8C,E). The stance trajectories were found to be parallel to the treadmill velocity vector and the body axis (data not shown), suggesting that backward walking was well adapted to the treadmill motion. Similar results were obtained in all backward walking cats. Backward walking was observed in four of seven tested animals (Table 1, column 180°).

If the treadmill belt did not move, SC stimulation evoked in cat 2 "in-place stepping" (Fig. 8 F,G), characterized by the following: (1) alternating EMG activity of the right and left limbs (period ~1 s), (2) reciprocal flexor and extensor bursts in each limb, (3) vertical oscillations of the foot that resulted in the periodicity of a ground reaction force under the limb, and (4) absence of horizontal foot displacements during the movement cycle (Fig. 8G). In-place stepping was observed in four of six tested cats. In two cats, in-place stepping of only one limb was observed. In all four cats, in-place stepping limb movements had characteristics similar to those in cat 2.

If the treadmill supporting the limbs was removed, both MLR stimulation and SC stimulation could evoke "air stepping," but characteristics of limb movements under these two conditions were very different. Figure 9A shows one cycle of air stepping in cat 4 with MLR and SC stimulation. One can see that the magnitude of limb oscillations (angle between extreme anterior and posterior limb positions, S) was much larger with MLR stimulation than with SC stimulation, whereas the cycle duration with MLR stimulation was shorter. When averaged over all cats exhibiting air stepping, these values were significantly different: the magnitude of oscillations was 44 ± 15° against 16 ± 5°, and the cycle duration was 0.51 ± 0.11 s against 0.81 ± 0.22 s (Fig. 9B). The EMG patterns of air stepping under the two conditions also differed. Alternation of flexor and extensor bursts in each limb was seen clearer with MLR stimulation than with SC stimulation

(Fig. 9, compare C,D). With SC stimulation, in-phase bursts in antagonistic muscles were sometimes observed. Air stepping was evoked by MLR stimulation in three of four tested cats, and by SC stimulation in three of six cats.

Discussion

In the present study, we compared locomotion in decerebrate cats evoked by MLR and SC stimulation. MLR stimulation primarily activates brainstem locomotor circuits that, through descending pathways, activate and modulate individual spinal limb controllers (for review, see Arshavsky et al., 1986; Orlovsky et al., 1999). In contrast, stimulation of the spinal cord can immediately activate limb controllers (as demonstrated in spinal animals; Barthélemy et al., 2007; Courtine et al., 2009). One cannot exclude, however, that SC stimulation in decerebrate animals, through ascending pathways, can activate brainstem circuits sending commands to the spinal cord (spino-bulbo-spinal loop). Nevertheless, it seems likely that MLR- and SC-evoked locomotion strongly differ in the contribution of spinal and supraspinal mechanisms to activation and modulation of limb controllers. Comparison of forward locomotion in decerebrate cats, evoked by MLR and SC stimulation, was first done by Iwahara et al. (1992). They demonstrated a close similarity between two locomotor patterns. However, a striking difference between the two patterns was found in the present study when comparing locomotion not only forward but also in other directions.

We found that SC-evoked stepping could be oriented in different directions relative to the longitudinal body axis, depending on the direction of treadmill motion. Thus, the direction of stepping was determined by external conditions. Similar results were obtained in chronic spinal rats walking on the treadmill that moved backward, forward, or sideward (Courtine et al., 2009;
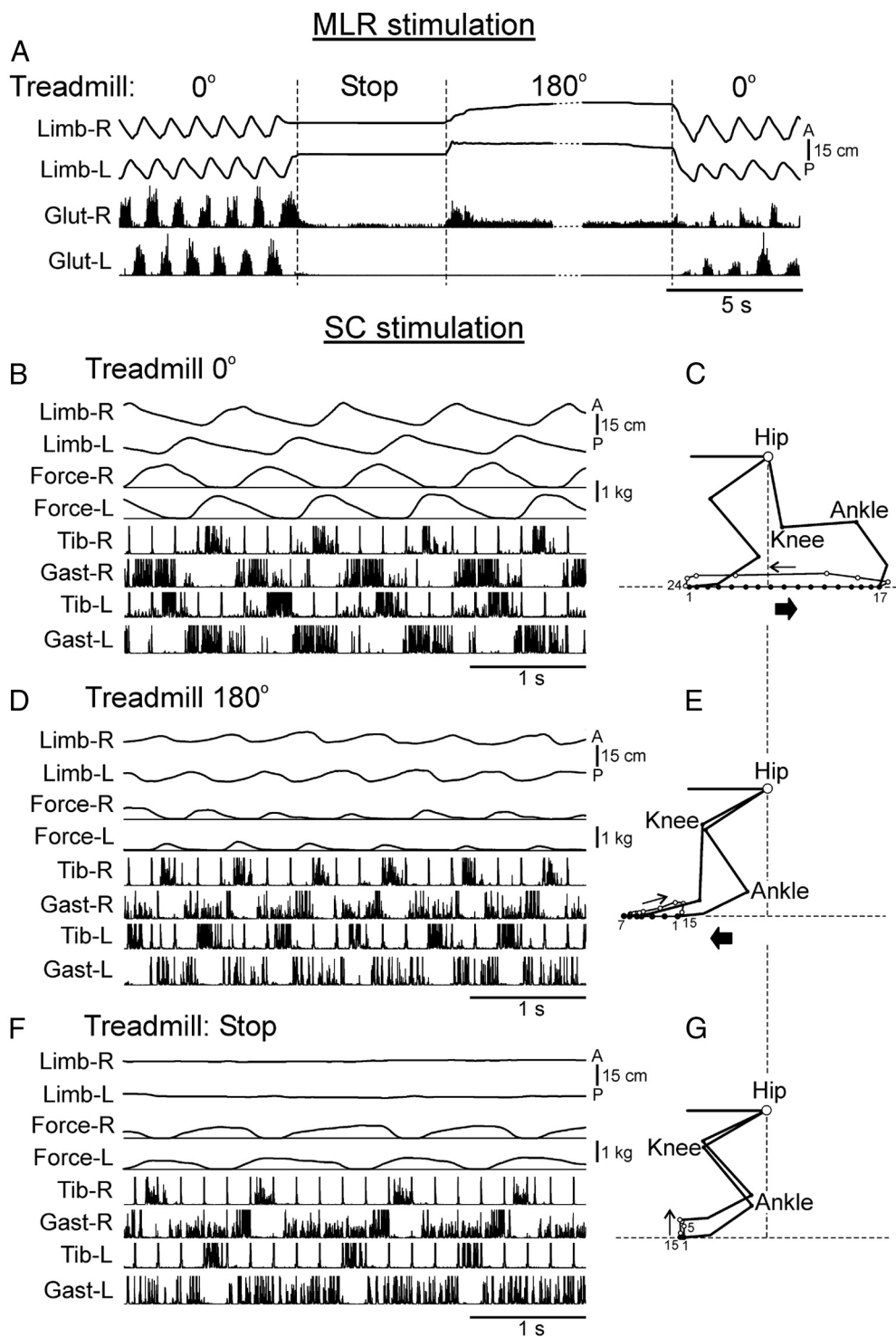
Figure 8. Comparison of locomotor effects of MLR and SC stimulation under different support conditions. ***A***, Example of the effects of MLR stimulation in cat 5 under three conditions: treadmill moved backward (0°), did not move (Stop), moved forward (180°) and then backward again (0°). ***B–G***, Examples of locomotor effects of SC stimulation in cat 2 under three conditions: treadmill moved backward (***B, C***), forward (***D, E***), and did not move (***F, G***). ***C, E, G***, Sequential positions of the left foot during one step cycle. Extreme limb positions are shown. Symbols and designations as in Figure 3.

Shah et al., 2012). SC-evoked backward locomotion was also observed in spinal and decerebrate cats (Gerasimenko et al., 2005; Musienko et al., 2007).

We found that SC-evoked stepping could be performed not only in the principal body planes and directions (forward, backward, and sideward) but also in the diagonal plane (45°; Fig. 6). This finding suggests that each limb controller can generate a

continuous spectrum of the forms of locomotion differing in the direction of stepping, rather than a few discrete forms. This view has been supported by the finding (Lamb and Yang, 2000; Pang and Yang, 2002) that infants (whose limb control mechanisms are situated at the lower CNS levels) are capable of stepping in different directions, with no discrete differences in either the EMG patterns or the temporal parameters of stepping, as the
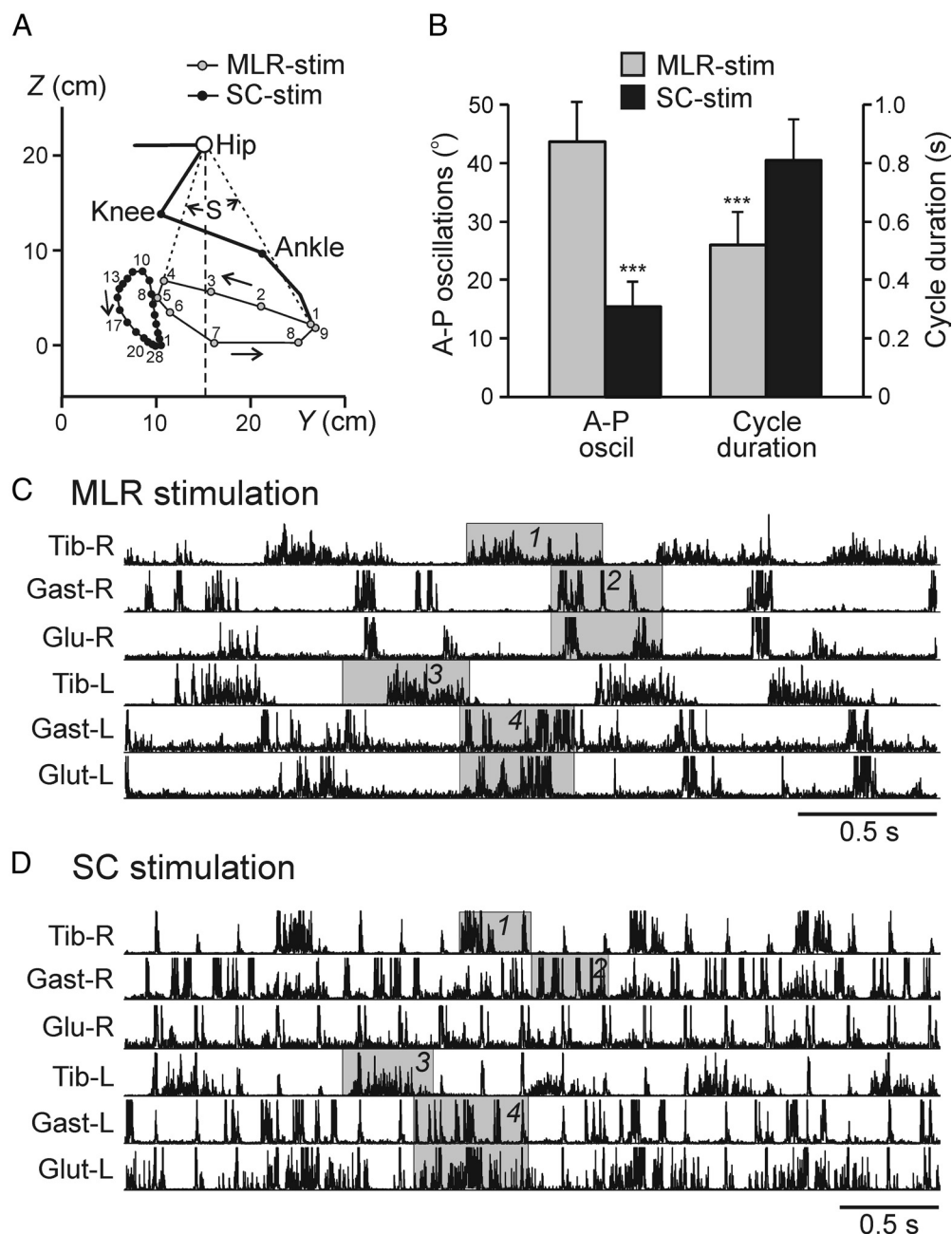
Air stepping

Figure 9. Comparison of air stepping evoked by MLR and SC stimulation. ***A***, Sequential positions of the right foot during one cycle of air stepping evoked by MLR stimulation (gray circles) and by SC stimulation (black circles) in cat 4. Arrows show the directions of foot movement. Angle *S* characterizes the magnitude of A-P oscillations (A-P oscil) of the limb. ***B***, Characteristics of air stepping averaged in three cats with MLR stimulation and in three cats with SC stimulation, over 36 and 59 step cycles, respectively (mean ± SD; indication of significance level: ***$p < 0.001$). ***C***, ***D***, EMG activity during air stepping evoked by MLR stimulation (***C***) and SC stimulation (***D***). The phases of flexor activity (1 and 3) and extensor activity (2 and 4) are highlighted. Symbols and designations as in Figures 2 and 3.

direction of stepping was gradually changed. A large diversity of the directions of stepping is characteristic for many other legged animals, e.g., crustaceans (Larimer, 1976; Ayers and Clarac, 1978).

In contrast to SC stimulation, MLR stimulation evoked coordinated stepping movements only if the treadmill was moving in the front-to-rear direction (Fig. 2A). With all other angles of treadmill motion, stepping movements were dramatically distorted or absent (Figs. 5A, 6A, 8A). The analysis of these distortions suggests that the limb controllers, when activated from

MLR, generate motor commands for forward stepping, irrelevant to treadmill motion.

These suggestions were supported in air stepping experiments. During air stepping evoked by MLR stimulation, the limb controller generates limb oscillations with a large A-P component (Fig. 9A,B), comparable to the step length during treadmill forward walking (Fig. 2A). We suggest that the spinal circuits generating this A-P component are activated by MLR-evoked supraspinal commands during treadmill locomotion as well, and thus determine the forward direction of walking.
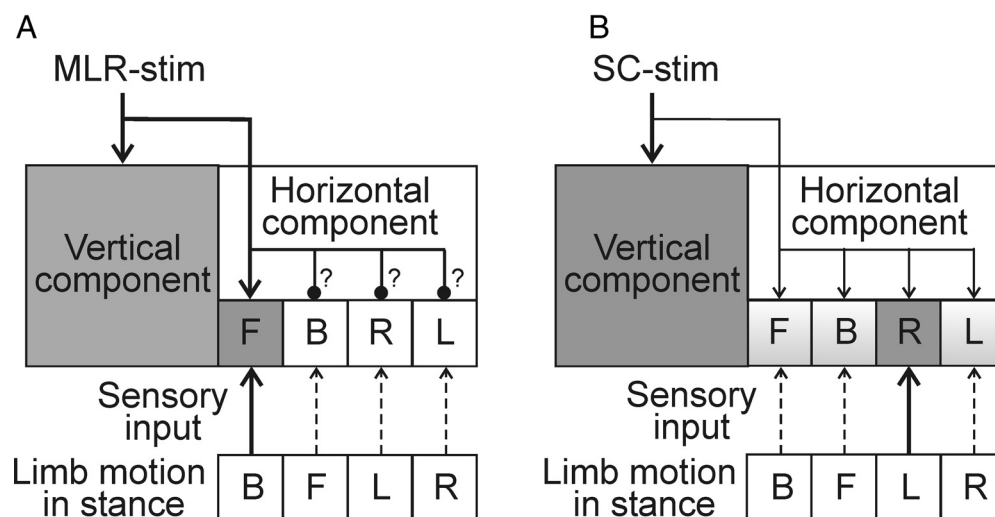
Figure 10. Basic mechanisms for the control of step direction. ***A***, Elicitation of stepping by MLR stimulation. Question marks indicate inhibitory connections that are not a necessary condition for the model functioning. ***B***, Elicitation of stepping by SC stimulation. Activation of a given mechanism, gray; subthreshold activation, light gray; inhibition, white. See Discussion for explanation. F, forward; B, backward; R, rightward; L, leftward.

In contrast, during air stepping evoked by SC stimulation, the limb controller generates much smaller limb oscillations, without a large component in A-P direction (as in MLR-evoked air stepping, Fig. 9*A*,*B*) or in any other horizontal direction. The horizontal component was practically absent during in-place stepping (Fig. 8*F*). Thus, SC stimulation itself does not cause any directionality in the limb trajectory. A large horizontal component in limb oscillations appears only after positioning the limb on the moving treadmill, and the direction of treadmill motion (monitored by sensory input from the limb during stance) determines the direction of stepping. This is not possible in MLR-stimulated cats, in which the forward direction of stepping is determined by supraspinal commands.

The MLR can thus be considered as a command center for elicitation of forward locomotion. This form of locomotion is vitally important for animals and humans as the main form of subject's progression. We suggest that function of supraspinal commands, initiated by MLR stimulation and transmitted by descending pathways, is to select and activate only one of numerous forms of operation of limb controllers, namely, forward walking. The viewpoint that different motor patterns can be produced by the same circuitry given the appropriate modulatory mechanism was considered by a number of authors (Gelfand et al., 1988; Marder and Calabrese, 1996; Shah et al., 2012). One can hypothesize that some other forms of locomotion (e.g., backward and sideward walking) also have their command centers.

As shown in the present study, walking in different directions evoked by SC stimulation is accompanied by considerable changes in the pattern of limb movements and muscular activity. First, during stepping that includes a lateral component (sideward and diagonal walking), the leading and trailing limbs have very different motor patterns, including the step magnitude and EMG profiles (Figs. 5*C*,7*B*). Second, the functional role of individual muscles may radically change, depending on the direction of stepping. For example, the right hip adductor (Fig. 7*B*, Add-R) may contribute to the transfer of the right limb during leftward walking, but to the stance of this limb during rightward walking. The contribution of a given muscle to the limb transfer or to the limb stance may change gradually when the direction of stepping is changing, as, e.g., in Glut-R (compare Fig. 7*B*, Glut-R at α = 0,

45, and 90°). Gradual changes in EMG patterns when walking in different directions were earlier demonstrated in human infants (Lamb and Yang, 2000; Pang and Yang, 2002). However, for a comprehensive description of limb stepping in different directions, one needs much more information about activity of numerous limb muscles, movements at different joints, etc.

Analysis of forward walking in the spinal cat exposed a number of neural mechanisms responsible for the transition from one phase of the step cycle to the other phase (e.g., Grillner and Rossignol, 1978). A critical point in the step cycle is onset of the swing phase. The most important factor for triggering swing is reaching by the limb a definite caudal position (e.g., a critical angle of hip extension). The other factors include unloading the limb, influences from the opposite limb, influences from the central pattern generator (Grillner, 1973, 1975; Grillner and Zangger, 1979; Orlovsky et al., 1999), etc. To extend this concept of swing generation on other directions of stepping, one can suggest that the swing onset is determined by the afferents signaling a critical limb deviation in the stance phase. For example, during sideward walking, the afferent signals about hip adduction and abduction could be used for triggering the swing in opposite direction.

Steps in different directions are often used by animals and humans for the maintenance of balance during standing and during locomotion. Large postural perturbations during standing, caused by lateral tilt of the support or lateral push, can elicit lateral step in rabbit and cat (Beloozerova et al., 2003; Karayannidou et al., 2009). A step with lateral component can also be elicited by a large postural perturbation in standing humans (Chvatal et al., 2011). Also, in the cat walking forward, a step deviated from the direction of progression (to the right or to the left) is used for correcting the perturbations of balance (Karayannidou et al., 2009). One can suggest that common spinal mechanisms are used for the generation of a single step during postural corrections, as well as for the generation of repetitive steps during locomotion.

To conclude, we propose a hypothesis about control of step direction (Fig. 10*A*). A limb controller (Orlovsky et al., 1999) includes two principal mechanisms, one generating a vertical component of step (limb elevation and lowering), and the other generating a horizontal component (limb transfer from one ex-

treme point to the other). The latter includes circuits generating the horizontal component of step in different directions (for simplicity, Fig. 10 shows only the circuits generating steps in four directions: F, forward; B, backward; R, rightward; L, leftward). These circuits receive sensory input signaling limb motion in stance; reaching an extreme position triggers a limb transfer.

MLR stimulation (Fig. 10A) activates a mechanism generating the vertical component of step, selects and activates the circuit F that will transfer the limb forward during swing and backward during stance, and possibly inhibits all other circuits (B, R, and L). The sensory input signaling backward limb deviation during stance assists triggering the limb transfer. Thus, MLR stimulation evokes forward stepping independently of the direction of treadmill motion.

SC stimulation (Fig. 10B) activates a mechanism generating the vertical component of step. It also causes subthreshold activation of all circuits generating the horizontal component. Due to the treadmill motion (e.g., to the left), the limb will reach an extreme left position, and sensory input will activate circuit R, which will evoke rightward step. Thus, SC stimulation can evoke stepping opposite to treadmill motion.

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